

A retrospective analysis of the mortality, and the perinatal risk factors for mortality, of very low birth weight infants admitted to Universitas Academic Hospital over a 2-year period – January 2016 to December 2017

By

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Declaration of Authorship

I, Dr. N.S. De Abreu, declare that the mini-dissertation that I herewith submit in a publishable manuscript format is my independent work. No previous submissions for a qualification at another institution of higher education has been made.



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| Author | Role in study |
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| Mr. C. Van Rooyen | Statistical supervision, data analysis. |

There is no conflict of interest to be declared by any of the authors. No other situation of real, potential or apparent conflict of interest is known to them. The university will be informed should there be any change in these circumstances.

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DEDICATION

I wish to dedicate, with much love and appreciation, this research to my Mother and Late Father – people in my life who not only dreamt the world for me, but managed to provide me the world, and who are my world.

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Abstract

Background: A rise in preterm deliveries of very low birth weight (VLBW) infants, less than 1 500 grams, is currently introducing a global public health dilemma. VLBW infants are at increased risk for morbidity and mortality. Identifying and addressing perinatal risk factors in order to improve the prognosis of VLBW infants are fundamental.

Objectives: The *primary objectives* of this study were to determine mortality rate and disease profile of VLBW infants admitted into the neonatal unit at Universitas Academic Hospital (UAH). The *secondary objective* was to determine perinatal factors which impacted the mortality of VLBW infants.

Methods: A retrospective analytical cross-sectional study was conducted. Study participants, namely VLBW infants, were identified by making use of admission registries, electronic and paper patient records. This data was then used to identify causes of mortality, and perinatal risk factors that increased the risk of mortality.

Results: Mortality of VLBW infants was 25.3%. The main causes of mortality were pulmonary haemorrhage (26.3%), necrotising enterocolitis (20%), multi-organ prematurity (20%) and intraventricular haemorrhage (3.8%). Male gender, low birth weight, low gestational age, no antenatal steroids received, hypothermia, surfactant administration, and the need for ventilation were all factors associated with increased mortality. Metabolic acidosis and hyperlactataemia also demonstrated a strong association with mortality.

Conclusion: Survival rates of VLBW infants compare favourably with tertiary hospitals in South Africa and developing countries. Basic interventions, such as improving antenatal care and avoiding neonatal hypothermia, and limiting risk factors associated with pulmonary haemorrhage will minimise the mortality risk. Policy change, regarding admission of infants weighing more than 900 grams to intensive care, should be considered to allow escalation of care to improve survival.

Keywords and Definitions

Antenatal care

- The care of the mother and infant throughout pregnancy, prior to delivery.

Antenatal steroids

- The medication that is administered to pregnant women in preterm labour, prior to delivery, to reduce the morbidity and mortality related to respiratory distress syndrome.

Apgar score

- Scores that are recorded at 1 and 5 minutes after birth that indicate the overall wellbeing of the new-born.

Early neonatal death

- The death of a neonate within the first 7 days of life.

Extremely low birth weight infants

- Newborn infants born with a weight less than 1 000 grams.

Gestational Age

- The period, in weeks, of how advanced the pregnancy is. This is calculated from the first day of the last normal menstrual period.

High frequency oscillatory ventilation

- Unconventional mechanical ventilation using respiratory rates four times the normal value with very small tidal volumes.

Kangaroo mother care

- Skin-to-skin contact whilst the mother holds her infant on her bare chest.

Late neonatal death

- The death of a neonate occurring after 7 days but before 28 completed days of life.

Mechanical ventilation

- The technique through which gas is moved toward and from the lungs through an external device connected directly to the patient.

Nasal continuous positive airway pressure - A form of positive distending airway pressure where mild air pressure is applied on a continuous basis to keep the airways continuously open.

Neonatal

- Newborn infants who are less than 28 days of age.

Neonatal mortality rate

- The number of newborn infants who demise within the first 28 days of life. This is expressed per 1 000 live births.

Prematurity

- A premature birth is one that occurs before the start of the 37th week of pregnancy.

Sepsis

- A life-threatening condition that results in multi-organ dysfunction. This is caused by a dysregulated host response to infection.

Small for gestational age

- Newborn infants who are born with a birth weight below the 10th percentile on the Fenton growth chart

Surfactant therapy

- The medical administration of exogenous surfactant with the purpose of decreasing surface tension within the alveoli of the lung.

Very low birth weight infants

- Newborn infants born with a weight less than 1 500 grams. This includes extremely low birth weight infants.

List of Abbreviations

| | | |
|-----------|---|--|
| C-Section | – | Caesarean section |
| CHBH | – | Chris Hani Baragwanath Hospital |
| CMH | – | Charlotte Maxeke Hospital |
| ELBW | – | Extremely low birth weight |
| ENND | – | Early neonatal death |
| HFOV | – | High frequency oscillatory ventilation |
| IVH | – | Intraventricular haemorrhage |
| LNND | – | Late neonatal death |
| NCPAP | – | Nasal continuous positive airway pressure |
| NEC | – | Necrotising enterocolitis |
| NICU | – | Neonatal intensive care unit |
| NMR | – | Neonatal mortality rate |
| NVD | – | Normal vaginal delivery |
| RDS | – | Respiratory distress syndrome |
| PIPP | - | Perinatal Problem Identification Programme |
| SBAH | – | Steve Biko Academic Hospital |
| SGA | – | Small for gestational age |
| NHCU | – | Neonatal high care unit |
| UAH | – | Universitas Academic Hospital |
| UFS | – | University of the Free State |
| VLBW | – | Very low birth weight |

Chapter 1

Literature review

Approximately 130 million children globally are born annually. Of these an estimated 15 to 18 million of these children are prematurely born (i.e. a gestational age less than 37 completed weeks). ^[1,2] This translates to more than 1 in 10 infants being born prematurely, with this global statistic rising each year. ^[2] 14.0 % of infants that are born prematurely are born with a very low birth weight (VLBW), a birth weight which is less than 1 500 grams. ^[1,2] This weight category represents a vulnerable population group, with the risk of mortality reported as being 200 times more likely than those born with a normal birth weight of greater than 2 500 grams. ^[3]

Of the worldwide deaths among children under the age of 5 years in 2016, 46.0 % of deaths occurred in the neonatal period (i.e. within the first 28 days of life). 60.0 – 80.0% of neonatal deaths occurred in those that were born with a VLBW. ^[1] South Africa's annual reduction rate for under 5-mortality has remained low at 1.4% from 1990 to 2012. ^[4] All these overwhelming statistics, together with the increase in the South African neonatal mortality rate (NMR) from 11 per 1 000 live births to 12.4 per 1 000 live births in 2013 and 2016, respectively, have clearly contributed to the failure of South Africa achieving the target set for the Millennium Development goal, particularly Goal 4, of decreasing childhood mortality by two-thirds by the year 2015. ^[5]

The mortality rates of VLBW infants around the world can be differentiated between those seen in developed countries, with unlimited access to resources (e.g. The United States of America and European Countries), and those seen in developing countries (e.g. Iran, India and South Africa), where life-saving resources and equipment are not always readily available. VLBW infant mortality in developed countries such as Italy have been reported to be 19.6 %; resource limited countries such as India has reported a mortality rate of 33.3 % in VLBW infants, with Iran and Jamaica reporting a mortality rate of 50.0 % and 57.1 %, respectively. ^[5] Mortality rates of those born weighing less than 1 000 grams, i.e. extremely low birth weight (ELBW) infants, are higher in developing countries than developed countries, with rates of 73.4 % in Iran, 56.1 % in Italy and 48.0 % in the United States. ^[5] ELBW infant mortality in South Africa has been shown to be approximately 65.0 %, reflecting that only 1 in 3 ELBW infants are likely to survive. ^[6]

In South Africa, similar studies have been performed. At Charlotte Maxeke Hospital (CMH) situated in Johannesburg, a study comparing the morbidity and mortality of VLBW infants over 2 different periods, i.e. 2006/2007 and later in 2013, has shown mortality rates of 29.8% and 26.6%, respectively. ^[6] In 2015 in the Limpopo Province, at Mankweng Hospital, a similar mortality rate was demonstrated in VLBW with a mortality rate of 22.6%. ^[7] These are consistent with mortality rates of other developing countries. However, limited evidence is available showing the mortality rate, and data pertaining to morbidity, of VLBW infants in the Free State Province and Universitas Academic Hospital (UAH).

The South African Perinatal Problem Identification Programme (PIPP) is an important national tool in addressing the struggle that is neonatal morbidity and mortality. ^[4] The primary outcome of PIPP is to identify the total number and causes of neonatal deaths and, to identify the obstetric conditions contributing to perinatal morbidity and mortality. ^[4] The secondary outcome of this programme is to identify avoidable factors that may have impacted patient mortality. This then enables state facilities to identify crucial gaps, allowing for decisions to be made on where interventions are needed, such as equipment availability and staff training. ^[4] It is a tool that allows for monitoring of the progress made by health care facilities, and inversely, the issues that need to be addressed to improve neonatal outcomes. Not only are audits essential tools in aiding interventions in decreasing mortality, but audits are also important in improving the quality of care provided to both mother and child. ^[4] Literature has confirmed the importance of perinatal mortality audits, reflecting a 30% reduction in perinatal deaths. ^[4]

Data from the PIPP programme, together with various published literature, have shown that the predominant cause of death in VLBW infants is related to infant immaturity. This includes clinical diagnoses of pulmonary haemorrhage, respiratory distress syndrome (RDS), necrotising enterocolitis (NEC) and intraventricular haemorrhage (IVH). ^[1,6] Sepsis, perinatal asphyxia, congenital abnormalities and infant immaturity make up the 4 causes of neonatal mortality. These causes are consistent with various studies conducted in South Africa. ^[6,7,8] At Chris Hani Baragwanath Hospital (CHBH), immaturity accounted for 63.0 % of deaths. ^[8] At Steve Biko Academic Hospital (SBAH) and CMH, mortality due to immaturity accounted for 43.0 % and 40.0 % of deaths, the top cause of death at both of these Johannesburg-based institutions. ^[1,6] Sepsis accounted for approximately 27.0 % of deaths at both CHBH and SBAH. ^[1,6]

Multiple studies have investigated the various perinatal risk factors and predictors of mortality. Birth weight and gestational age display an inverse relationship with mortality. [3,9] Mortality rates have shown to increase with decreasing gestational age and birth weight. [3,9] The greatest mortality rate is seen in ELBW infants and in those born with a gestational age of less than 32 weeks. [3,9]

Scoring systems, such as the Clinical Risk Index for Babies (CRIB II), have used perinatal factors in assisting to predict mortality, particularly in infants with a VLBW. [10] This scoring system uses the commonly known factors associated with mortality, namely gestational age and infant birth weight, but have also considered gender, the presence of hypothermia and an arterial blood gas within an hour of admission. [10] Scoring systems, such as the CRIB II score, have specifically defined parameters for acidosis and hyperlactataemia that can be used for research purposes.

Other important factors shown to impact mortality rates can be grouped into different categories: Maternal factors; delivery related factors; and neonate related factors. [6]

Maternal factors that contribute to the mortality and morbidity in neonates include that of maternal age, the maternal condition that categorises the pregnancy as high risk, the presence of maternal infection (e.g. chorioamnionitis) and whether the mother attended their local clinic or high-risk center antenatally. [6,7,11]

Those infants born to teenage mothers (18 years of age and younger) and mothers with advanced maternal age (35 years of age and older) have been shown to have an increased association with neonatal mortality. [11]

Maternal illness has shown to have an impact on the outcomes of neonates. These conditions include those of maternal hypertension, diabetes, the presence of chorioamnionitis and HIV infection – all of which place newborns at a higher risk for mortality. [6,11] Pregnancy-induced hypertensive disease is one of the leading causes of maternal mortality, and has shown to impact neonatal mortality. [12]

A meta-analysis of 55 sites from 25 countries confirmed that pregnancy-induced hypertensive disease is related to adverse maternal and neonatal outcomes, and is the leading reason for emergency caesarean sections (C-sections), and subsequent preterm delivery. ^[12]

With regular attendance at antenatal clinics and subsequent regular follow-ups, neonatal mortality has shown to decrease. ^[6,8] Antenatal care allows for mothers who are at high risk of preterm labour to be identified early on in their pregnancies. In so doing, early and appropriate referrals to more specialised centres equipped with obstetric services and neonatal intensive care facilities are possible, contributing to a reduction in mortality rates.

Respiratory distress syndrome (RDS), a condition resulting from lung immaturity and surfactant deficiency, is a common cause of neonatal mortality. ^[13] The administration of steroids to a pregnant woman at risk of preterm delivery, and the subsequent administration of rescue doses of surfactant, contribute to a lower mortality rate. ^[13] The early use of surfactant, within the first 2 hours, is associated with mortality reduction as compared to the late administration of surfactant. ^[13] A single course of antenatal steroids given to mothers in preterm labour, at a gestation of less than 34 weeks, significantly reduces the incidence of RDS and that of neonatal deaths by 31.0 %. ^[13] Other benefits of using antenatal steroids are the reduction in the incidence of IVH by 46.0 %, and a 54.0 % reduction in NEC. ^[13] South Africa has adopted the policy of antenatal steroid use in pregnancy duration of less than 34 weeks' gestation.

Premature infants born by caesarean section (C-section) have a lower mortality rate compared to those born by normal vaginal delivery (NVD). ^[6,14] This signifies the early detection of high-risk pregnancies and fetal distress cases, allowing for urgent and emergent C-section deliveries to avoid complications seen with normal vaginal deliveries.

Mortality rates have also shown to be higher in those born before arriving at a medical facility, as opposed to those born at a clinic or hospital. ^[6] Furthermore, a greater risk of mortality has been noted in patients who were referred in from other institutions (i.e. out born patients) versus those that were born at a tertiary level facility. ^[6,14] This is likely secondary to the limitation of essential equipment and trained staff at peripheral clinics and health care facilities, and the delayed arrival of patients given the large burden on a somewhat limited emergency response system.

Neonate-related factors that contribute to increased morbidity and mortality include gestational age, birth weight, admission hypothermia, hypoglycaemia, acidosis as well as low Apgar scores.

Hypothermia on admission has been shown to be an independent risk factor for mortality.

^[13] With regards to arterial blood gas, the greater the base deficit, a greater risk for mortality has been shown. ^[10] Male newborns, who have an increased risk of RDS, have been shown to have a greater risk of mortality compared to female newborns, particularly when born prematurely. ^[8]

The Apgar scores at 1 minute and 5 minutes after birth are associated with patient outcomes. An Apgar score of less than 6 at 5 minutes has been shown to increase the risk of mortality. ^[8,14] However, the Apgar score alone cannot be used to predict neonatal mortality, and is an accepted method of reporting the status of the newborn immediately after birth, and the response to resuscitation if needed.

Hypoglycaemia is the most frequent metabolic abnormality in the newborn. ^[15] Hypoglycaemia occurs in 1.3 to 4.4 per 1 000 term newborns and 15 to 55 per 1 000 preterm newborns, suggesting that gestational age and prematurity are risk factors for hypoglycaemia. ^[15] This is in part due to the inadequately developed adaptive mechanisms in preterm infants which predispose them to an increased risk of hypoglycaemia. ^[15] The prevalence of hypoglycaemia has been shown to be approximately 10.0 % in term neonates; 6.5 % in appropriate for gestational age (AGA), 8.0 % in large for gestational age (LGA), and 15.0 % in small for gestational age (SGA) newborns. ^[15] Literature has shown that 15.5 % of late preterm infants have hypoglycaemia on admission. ^[15] Hypoglycaemia, as an independent factor, has however not been shown to be associated with an increase in neonatal mortality. ^[15]

The initiation of respiratory support, in those who would otherwise not qualify for intubation and mechanical ventilation, is another factor shown to improve outcomes in VLBW neonates. ^[6,13]

Nasal continuous positive airway pressure (NCPAP) has shown to reduce the need for intubation and mechanical ventilation by 38.0 %. NCPAP also reduces respiratory failure and subsequent death by 35.0 %.^[10,13] NCPAP is simple to use, does not require specialised intubation skill and is non-invasive. This makes NCPAP an appropriate mode of respiratory support that can be used outside the neonatal intensive care unit (NICU).^[1,6,8,13]

In resource-limited areas and developing countries, the belief that only modern, expensive interventions such as conventional ventilation and high frequency oscillatory ventilation (HFOV), can improve neonatal outcome is not appropriate.^[1]

With interventions such as antenatal steroids, NCPAP, and the early administration of surfactant, together with in-expensive and cost-effective interventions such as providing kangaroo mother care, administering breast milk and preventing hypothermia and hypoglycaemia, the expectation for a reduced mortality rate in VLBW infants should be a practical expectation, rather than a goal.^[1,13]

The focus globally is now to work towards attaining the 2025 Born Too Soon goal of achieving a 50.0 % reduction in the under-5 mortality rate.^[2] A continued focus on the National Perinatal Morbidity and Mortality Committee (NaPeMMCo) recommendations for saving babies should continue to be adopted.^[16] They summarised it as HHAPINESS, where HHAPI is an acronym used to summarise key recommendations needed to improve newborn care and neonatal survival.^[16] This includes: improving the *health* system for mothers and babies; improving the skills of *health* care practitioners in maternal and neonatal care; and reducing the deaths attributed to *asphyxia, prematurity and infection*.^[16]

Given that prematurity contributes significantly to childhood mortality, the focus should be decreasing preterm deliveries of infants, and to evaluate current statistics, be it at individual institutions, nationally or provincially. With a focus on neonatal mortality and the factors that contribute to this mortality, clinicians and policy makers can focus on providing interventions and services towards limiting these factors, and thereby improving survival of this vulnerable population group.

This study was conducted at the Universitas Academic Hospital Complex in Bloemfontein, South Africa, which serves the entire Free State Province. The Academic complex also accepts referrals from the Northern Cape and Lesotho.

Unit Facilities

The obstetric unit functions as a high care unit. Pregnant women with maternal or fetal conditions placing them at high risk are admitted to UAH, where their infants are subsequently delivered. Maternal conditions placing pregnant women at high risk include those of gestational hypertension, pre-eclampsia and the subsequent syndrome consisting of haemolysis, elevated liver enzymes and low platelets (i.e. HELLP syndrome). Other conditions include maternal cardiac conditions such as rheumatic heart disease with valvular pathology, cardiac failure, gestational diabetes and maternal seizures. Pregnant women admitted to the Obstetric Unit are at times critically ill and represent a different clinical picture compared to those who present at peripheral medical facilities.

The neonatal unit consists of three different divisions, and is so divided according to the provision of interventions and the level of care required. These 3 units admit around 600 neonates per year, approximately 150 of whom are VLBW infants.

A 14-bed neonatal intensive care unit (NICU), offering invasive ventilation and HFOV. There is a standardised protocol stating that infants born greater than 1 000 grams who require intubation will be admitted to the NICU.

However, admission to the NICU is on a case by case basis. Infants born less than 1 000 grams may be considered for NICU admission and mechanical ventilation depending on the resources and number of staff available. Maternal history, the fetal well-being during labour and the response to newborn resuscitation are also taken into account.

In 2017, the NICU was subdivided into three different cubicles. These cubicles include those providing care for patients with medical conditions, pre- and post-surgical patients and an isolation cubicle where patients with proven sepsis are isolated. This has been established in an attempt to decrease the sepsis rate in this unit.

The neonatal high care unit (NHCU) has no restrictions for admission with regards to birth weight. Bed capacity in this unit is 16. The provision of NCPAP and high flow nasal oxygen is readily available.

The neonatal ward functions as a unit for those patients with no, or resolved, acute ailments and those nearing discharge. This ward usually accommodates those infants greater than 1 500 grams requiring little to no intervention, and usually experiences the greatest turnover.

The problem addressed with this study is that of limited local data pertaining to the mortality of VLBW infants at UAH. By quantifying mortality in this vulnerable population, together with identifying risk factors contributing to mortality, informed decisions can be made. Provision of resources and targeted interventions to benefit those with improved outcomes should be prioritised. This is particularly important in a resource-limited setting, as experienced in UAH and South Africa.

Study Objectives

The aim and primary objective of this study was to determine the mortality rate and disease profile of very low birth infants admitted to the neonatal unit at UAH from 1 January 2016 to 31 December 2017.

The *primary objectives* of this study were to determine the mortality rate and disease profile of VLBW infants admitted into the Neonatal Unit at Universitas Academic Hospital (UAH). The *secondary objective* was to determine perinatal factors which impacted the mortality of VLBW infants.

This study will positively impact the neonatal unit, UAH, the Free State Department of Health and most importantly, the parents of premature infants admitted to the unit. The information gathered better informs the unit as to what the causes of death are, thereby focusing interventions in preventing and reducing mortality. It provides information regarding which interventions should be available in the neonatal unit to prevent mortality in this population.

Results from this study will better assist in drafting policies, allowing the justification by health practitioners regarding the restriction or provision of interventions in certain weight categories secondary to limitation of resources.

With regards to parents of VLBW and ELBW infants, such a study will allow for appropriate counselling on expectations, in terms of morbidity and mortality, and better prepare parents for the course of their baby's admission in a neonatal unit, and ultimately their prognosis.

Limitations of the Study

There are a number of limitations of performing a retrospective study. Patient selection for this study relied solely on admission registries, patient records and the quality of notes formulated. Inaccurate recording or capturing of patient information, as well as capturing of the incorrect patient diagnosis may have had an effect on the data collection process. Incomplete records and failure to record pre-natal and post-natal factors to be reviewed in this study may have potentially impacted this study. Lost records also had a small impact on this study. In a resource-rich setting, with sufficient time and manpower, a prospective study would be recommended. However, in our setting, a great focus is placed on meeting critical clinical services in our central care unit.

This study was conducted in a central facility. The data may therefore not be reflective of neonatal survival or mortality outcomes in secondary level hospitals. A similar study in secondary level hospitals should be performed. Comparing mortality and survival rates in VLBW infants of secondary and tertiary level hospitals would help to identify factors contributing to mortality in secondary hospital facilities, which tertiary facilities may be able to address.

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Chapter 2

Abstract

Background: A rise in preterm deliveries of very low birth weight (VLBW) infants, less than 1 500 grams, is currently introducing a global public health dilemma. VLBW infants are at increased risk for morbidity and mortality. Identifying and addressing perinatal risk factors in order to improve the prognosis of VLBW infants are fundamental.

Objectives: The *primary objectives* of this study were to determine mortality rate and disease profile of VLBW infants admitted into the neonatal unit at Universitas Academic Hospital (UAH). The *secondary objective* was to determine perinatal factors which impacted the mortality of VLBW infants.

Methods: A retrospective analytical cross-sectional study was conducted. Study participants, namely VLBW infants, were identified by making use of admission registries, electronic and paper patient records. This data was then used to identify causes of mortality, and perinatal risk factors that increased the risk of mortality.

Results: Mortality of VLBW infants was 25.3%. The main causes of mortality were pulmonary haemorrhage (26.3%), necrotising enterocolitis (20%), multi-organ prematurity (20%) and intraventricular haemorrhage (3.8%). Male gender, low birth weight, low gestational age, no antenatal steroids received, hypothermia, surfactant administration, and the need for ventilation were all factors associated with increased mortality. Metabolic acidosis and hyperlactataemia also demonstrated a strong association with mortality.

Conclusion: Survival rates of VLBW infants compare favourably with tertiary hospitals in South Africa and developing countries. Basic interventions, such as improving antenatal care and avoiding neonatal hypothermia, and limiting risk factors associated with pulmonary haemorrhage will minimise the mortality risk. Policy change, regarding admission of infants weighing more than 900 grams to intensive care, should be considered to allow escalation of care to improve survival.

Introduction

Globally, approximately 15 to 18 million infants are born prematurely with 14% of these infants being born with very low birth weights (VLBW) of less than 1 500 grams. ^[1,2] Of deaths in the under-5 age group in 2016, 46.0 % occurred in the neonatal period with 60.0 - 80.0 % of these deaths occurring in VLBW infants. ^[1,3] This, together with the increase in the South African neonatal mortality rate (NMR) from 11 per 1 000 live births to 12.4 per 1 000 live births in 2013 and 2016, respectively, contributed to South Africa failing to achieve the target set for the fourth Millennium Development goal of decreasing childhood mortality by two-thirds by 2015. ^[4] The focus globally is to attain the 2025 Born Too Soon goal of reducing the under-5 mortality rate by 50.0 %. ^[2] Prematurity contributes significantly to childhood mortality, therefore, the focus should be on decreasing preterm deliveries and improving the standard of neonatal care.

Mortality rates of VLBW infants range from 19.0 % in Thailand and Italy, 33.3% in India, to 57.0 % in Jamaica. ^[3] Mortality rates at Charlotte Maxeke Hospital (CMH) in Johannesburg, South Africa, were shown to be 29.8 % and 26.6 % in 2006/2007 and 2013, respectively. ^[5] In 2015 in the Limpopo Province, at Mankweng Hospital, a similar mortality rate was demonstrated in VLBW with a mortality rate of 22.6%. ^[6] Mortality rates of those born weighing less than 1 000 grams, i.e. extremely low birth weight (ELBW) infants, are higher with rates of 63.4 % in Iran, 56.0 % in Italy and 65.1 % in South Africa. ^[3] The predominant cause of death in VLBW infants is immaturity-related. These include clinical diagnoses of respiratory distress syndrome (RDS), pulmonary haemorrhage, necrotising enterocolitis (NEC) and intraventricular haemorrhage (IVH). Sepsis, perinatal asphyxia and congenital abnormalities round up the top 4 causes of neonatal mortality. ^[1,5,7]

Perinatal risk factors and predictors of mortality have been researched extensively and include those related to maternal factors (e.g. maternal age, infection and co-morbidity), delivery related factors (e.g. mode of delivery and delivery complications) and neonate-related factors (e.g. gender, hypothermia, hypoglycaemia, admission blood gas and Apgar scores). ^[3,5,7,8] This study was conducted at Universitas Academic Hospital (UAH) in Bloemfontein, South Africa to determine the mortality rate, and associated risk factors, of VLBW infants admitted from 1 January 2016 to 31 December 2017.

Methods

Study design

A retrospective analytical cross-sectional study was conducted. This study design enabled data such as birth weight, gestational age and known perinatal risk factors for morbidity and mortality in VLBW infants to be collected. A pilot study was initially conducted as a tool to assess the efficacy of the data capture sheet and the data capturing process.

Target population and population size

All VLBW infants admitted to the neonatal unit at UAH from 1st January 2016 to 31st December 2017 were included in the study. A total of 323 patient cases met the inclusion criteria for the study, however, 7 patient records/files from those included could not be found and these 7 cases were therefore removed from the study, leaving a sample size of 316 patient files for reviewing.

Data sources

Ethics clearance was obtained from the Health Sciences Research Ethics Committee (HSREC) at the University of the Free State prior to any data collection.

Study participants, namely VLBW infants, were identified by making use of admission registries, electronic and paper patient records. This data was then used to identify causes of mortality, and perinatal risk factors that increased the risk of mortality. All infants who were classified as VLBW infants at birth and on admission to the neonatal unit were included in this study, regardless of diagnosis or congenital abnormality. Still births and those who demised in the obstetric unit prior to admission to the neonatal unit were excluded from the study.

A pre-designed data capture form, formulated and based on the information gathered by the literature review, was used to collect relevant information. Data analysis was performed by a biostatistician at the Department of Biostatistics at the University of the Free State.

Confidentiality of patient information was prioritised. Only the primary investigator handled the patient files and data capture sheets in a private and secure location. A unique study number was allocated to each patient to protect his/her identity.

Results

A total of 323 cases were identified. However, 7 cases identified had no records available, other than the limited data from the admission registries. These 7 cases did not meet the inclusion criteria for this study and were removed, leaving a total sample size of 316 cases.

Maternal data

Maternal data was collected from 290 mothers. The median maternal age in this study was 28 years of age. Of all the mothers in the study, 58 (20.0 %) were classified as having an advanced maternal age (i.e. 35 years of age and older) and 9 (3.1 %) were teenage mothers (i.e. 18 years of age and younger). This was the first pregnancy for 75 (25.9 %) of the mothers of the neonates in this study (i.e. Primigravida). Despite being high-risk patients themselves, with varying co-morbidities, 25 (8.6 %) of the mothers did not access antenatal care. 29 (10%) of mothers had multiple pregnancies. All these factors had no association with mortality on statistical analysis.

Table 1. The top ten causes of maternal morbidity

| Maternal Morbidity | n (%) |
|--|--------------|
| Hypertensive disorders of pregnancy | 185 (58.5) |
| HIV | 128 (40.5) |
| Advanced maternal age | 87 (27.6) |
| Prolonged preterm rupture of membranes | 38 (12.0) |
| Chorioamnionitis | 34 (10.8) |
| No antenatal care | 25 (7.9) |
| Antepartum hemorrhage | 21 (6.7) |
| Poor obstetric history | 17 (5.4) |
| Diabetes mellitus | 10 (3.2) |
| Substance use/ misuse | 9 (2.9) |

Table 1 reflects causes of morbidity that are usually compounded by other risk factors that impact on neonatal mortality, suggesting that a mother could have 2 or 3 risk factors as mentioned above, placing their newborn at higher risk for mortality. The total number from the table does not reflect the number of mothers that undertook this study, but it identifies the total number of morbidity risk factors that were identified when collecting data from all the mothers.

The majority of deliveries, i.e. 254 (80.4 %), occurred at UAH, with the rest being referred from other facilities (Table 3). There was no evidence to suggest an association between mortality and whether the infant was born at UAH or elsewhere ($p=0.169$). Only 7 (2.2 %) of deliveries occurred before the arrival at a health care facility.

Regarding mode of delivery, 229 (72.5 %) of cases were delivered via caesarean section and 87 (27.5 %) via normal vaginal delivery (Table 3). A total of 62 cases (19.6 %) did not receive a single dose of antenatal steroids prior to preterm delivery (Table 3).

Neonatal data

Of all VLBW infants, 184 (58.2 %) were female (Table 3). However, with regards to mortality, male infants were more likely to die than female infants, with mortality rates of 31.0 % and 21.2 %, respectively. This was statistically significant ($p<0.0467$).

The mean birth weight was 1 120 grams, with 93 (29.4 %) classified as ELBW infants (Table 2). Infants with a birth weight less than 900 grams constituted 53 (16.8 %) cases (Table 2).

The mean gestational age was 29 weeks, with 279 (88.3 %) cases born between 27 and 32 weeks. Those born with a gestational age less than 26 weeks accounted for 17 (5.4 %) cases. A total of 97 (30.7 %) cases were classified as SGA (Table 3).

With regards to Apgar scores, 21 (6.6 %) had a score of less than 5 at 1 minute, and 10.0 % had Apgar scores of less than 5 at 5 minutes of life. An Apgar of less than 5 at 5 minutes had no statistical significance with regards to mortality ($p=0.8756$) (Table 3).

A total of 259 (82.0 %) VLBW infants were admitted to the NICU (Table 3). Medical cases made up 203 (78.2 %) of NICU admissions with 56 (21.8 %) cases being admitted for surgical interventions. VLBW infants who required invasive ventilation constituted 146 (46.2 %) cases, with 186 (58.9 %) cases requiring nasal continuous positive airway pressure (NCPAP) (Table 3). Surfactant was administered to 106 (33.7 %) VLBW infants.

Of VLBW infants admitted to the neonatal unit, 222 (70.3 %) were admitted with hypothermia, defined as a temperature of less than 36.5 degrees Celsius (°C) (Table 3). 175 cases (55.4 %) had a temperature of less than 36°C and 65 cases (20.6 %), the admission temperature was recorded as less than 35°C.

Hypoglycemia (i.e. glucose of less than 2.5mmo/L), was present on admission in 42.1 % of VLBW infants, with 26.6 % of cases having had an admission glucose of less than 2.0 mmol/L (Table 3).

The mean duration of stay for VLBW patients before discharge was 26.5 days, with the longest stay being that of 140 days. A total of 80 (25.3 %) VLBW infants admitted to UAH demised. 52 (65.4 %) of these deaths occurred in the first seven days of life (i.e. early neonatal death).

Table 2. Mortality and survival according to weight categories

| | Survival n (%) | Mortality n (%) | Total Births n (%) |
|---------------------|---------------------------|----------------------------|-------------------------------|
| < 900 grams | 23 (43.4) | 30 (56.6) | 53 (16.8) |
| 900 – 999 grams | 29 (72.5) | 11 (27.5) | 40 (12.7) |
| 1 000 – 1 499 grams | 184 (82.5) | 39 (17.5) | 223 (70.5) |
| Total Cases | 236 (74.7) | 80 (25.3) | 316 (100) |

Table 3. Perinatal risk factors and their association with mortality in VLBW infants

| Variable | | Category Total | Mortality n (%) | p-value |
|----------------------------------|--------|-----------------------|------------------------|----------------|
| Inborn | | 254 | 60 (23.6) | 0.1609 |
| Out born | | 62 | 20 (32.3) | |
| Gender | Male | 132 | 41 (31.1) | 0.0467 |
| | Female | 184 | 39 (21.2) | |
| Maternal HIV | Yes | 126 | 33 (26.2) | 0.7711 |
| | No | 190 | 47 (24.7) | |
| Antenatal care | No | 25 | 8 (32.0) | 0.4232 |
| | Yes | 291 | 72 (24.7) | |
| Antenatal steroids | No | 62 | 22 (35.5) | 0.0400 |
| | Yes | 254 | 58 (22.8) | |
| Advanced maternal age | Yes | 58 | 16 (27.6) | 0.6600 |
| | No | 258 | 64 (24.8) | |
| Small for gestational age | Yes | 97 | 29 (29.9) | 0.2127 |
| | No | 219 | 51 (23.3) | |
| Mode of Delivery | NVD | 87 | 25 (28.7) | 0.3889 |
| | C/S | 229 | 55 (24.0) | |
| 5-minute Apgar < 5 | Yes | 288 | 73 (25.4) | 0.8756 |
| | No | 21 | 5 (23.8) | |
| Hypothermia | Yes | 222 | 67 (30.2) | 0.0022 |
| | No | 94 | 13 (13.8) | |
| Hypoglycaemia | Yes | 114 | 48 (42.1) | 0.3977 |
| | No | 202 | 32 (15.8) | |
| Chorioamnionitis | Yes | 282 | 74 (26.2) | 0.2763 |
| | No | 34 | 6 (17.7) | |
| NICU admission | No | 57 | 20 (35.1) | 0.0609 |
| | Yes | 259 | 60 (23.2) | |
| NCPAP | Yes | 186 | 49 (26.3) | 0.6153 |
| | No | 130 | 31 (23.9) | |
| Ventilation | Yes | 146 | 55 (37.7) | <0.0001 |
| | No | 170 | 25 (14.7) | |

Admission blood gas

From the 316 cases for which patient data and files were found, a total of 53 cases did not meet the criteria of having a recorded admission blood gas within the first hour of life. These 53 cases were excluded for this component of the study, leaving a total of 262 cases to be reviewed. The results, as follows, confirmed the increased risk for infant mortality with the increased severity of acidosis and hyperlactataemia on admission.

12 (4.6 %) infants had an admission blood gas pH of < 7.0 . Of these infants, 10 (83.3 %) demised (Table 4). This proved to be statistically significant ($p < 0.0001$).

A base deficit of ≥ 7 mmol/L was also associated with an increased mortality ($p = 0.0003$). 115 (43.7 %) infants had a base deficit of ≥ 7 mmol/L, with the number of mortalities accounting for 61.2 % (41 of 67 infants). A base deficit of ≥ 15.0 mmol/L was associated with a mortality of 58.3 % (14 of 24 cases) (Table 4).

A total of 36 (13.7 %) infants had an admission lactate of > 9.0 mmol/L. Of these patients, 50.0 % (18) demised. In those who were admitted with a lactate of ≥ 14.0 mmol/L, 84.6% (11 of 13 cases) demised (Table 4). Hyperlactataemia proved to be statistically significant ($p < 0.0001$) as a risk factor for mortality in VLBW infants.

| Table 4: Admission blood gas and the association with mortality | | | | | |
|--|---------------------|----------------------|-------------------------|------------------------|-------------------|
| | | Total (n=263) | Mortality (n=67) | Total Mortality | p-value |
| | | n (%) | n (%) | n (%) | |
| pH | <7.0 | 12 (4.6) | 10 (14.9) | (10/12) 83.3 | <0.0001 |
| | 7.0 – 7.19 | 58 (22.1) | 21 (31.3) | (21/58) 36.2 | |
| | ≥ 7.2 | 193 (73.4) | 36 (53.7) | (36/193) 18.7 | |
| | | | | | |
| Base Deficit (mmol/L) | < 7.0 | 148 (56.3) | 26 (38.8) | (26/148) 17.6 | 0.0003 |
| | 7.0 – 14.9 | 91 (34.6) | 27 (40.3) | (27/91) 29.7 | |
| | ≥ 15.0 | 24 (9.1) | 14 (20.9) | (14/24) 58.3 | |
| | | | | | |
| Lactate (mmol/L) | < 9.0 | 227 (86.3) | 49 (73.1) | (49/227) 21.6 | <0.0001 |
| | ≥ 9.0 – 13.9 | 23 (8.8) | 7 (10.5) | (7/23) 30.4 | |
| | ≥ 14.0 | 13 (4.9) | 11 (16.4) | (11/13) 84.6 | |
| | | | | | |

Neonatal Mortality

The top cause of neonatal mortality was related to the immature state of preterm infants, accounting for 70.0 % of deaths (Graph 1). Of these cases, 26.3 % demised of a pulmonary hemorrhage, 19.9 % of necrotizing enterocolitis, 19.9 % of multi-organ prematurity, and 3.8 % of intraventricular hemorrhage. 18.7 % succumbed to sepsis.

Graph 1. Neontal Mortality

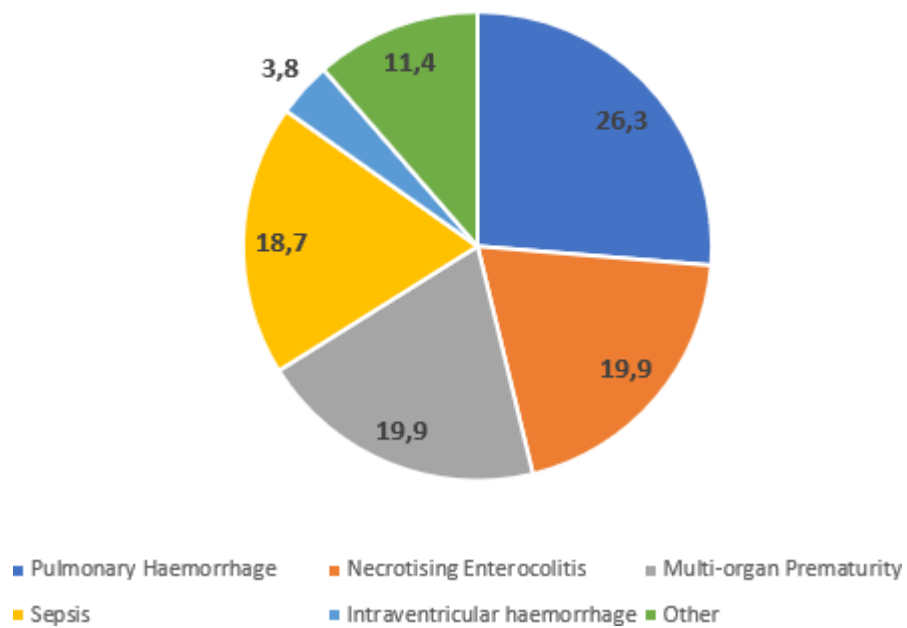


Table 5. The top ten causes of morbidity in VLBW infants

| Neonatal Morbidity | n (%) |
|--------------------------------------|--------------|
| Respiratory distress syndrome | 232 (73.4) |
| Neonatal jaundice | 122 (38.6) |
| Sepsis | 103 (32.6) |
| Congenital acyanotic cardiac lesions | 73 (23.1) |
| Intraventricular haemorrhage | 71 (22.5) |
| Perinatal asphyxia | 67 (21.2) |
| Necrotising enterocolitis | 48 (15.2) |
| Intrauterine growth restriction | 44 (13.9) |
| Anaemia | 39 (12.3) |
| Acute kidney injury | 28 (8.9) |

Table 5 reflects the common causes of morbidity in VLBW infants; however; many newborns do not demise with only one of this condition, but have a number of illnesses that contribute to their ultimate demise. Therefore, the total in Table 5 does not reflect a single diagnosis per case; but multiple diagnoses per case – therefore shifting the focus on the impact of the above conditions on neonatal mortality.

Discussion

This retrospective analytical study provides mortality rates and identifies perinatal risk-factors, both obstetric and neonatal, that have an association with mortality in VLBW infants at UAH.

The overall mortality rate of VLBW infants was 25.3 %, which is similar to other centres such as CMH, CBH and Mankweng Hospital who report survival rates of 24.6 %, 29.0 % and 22.6%, respectively.^[5,6] The majority of deaths, i.e. 52 (65.4 %), occurred within the first seven days of life; a statistic that compares with national and international data.^[3,5] Similar findings within our national framework reflects that with the rise in preterm deliveries and survival, international guidelines and protocols have been adjusted to the South African setting, with most centres using similar approaches in improving survival in VLBW infants.

A total of 93 ELBW infants were admitted to the neonatal unit (Table 2). 41 (44.1 %) demised. Our neonatal unit compared better with other central hospitals in South Africa reporting mortality rates of 65.1 % in ELBW infants, and other countries such as Iran and Italy with rates of 63.4 % and 56 %, respectively. A comparable mortality rate of ELBW has been reported in the United States (48.2 %).^[3]

Of the 40 patients that were born with a weight between 900 and 1 000 grams, 11 demised (27.5 %) (Table 2). This group had a more favourable prognosis when compared with neonates weighing less than 900 grams (mortality 56.6 %), justifying the admission of this weight category to NICU for intensive care and mechanical ventilation.

In 62 cases, of whom 11 did not receive antenatal care, no antenatal steroids were administered (Table 3). The reason for antenatal steroids not being administered was not clearly documented in patient records. However, possible reasons could include those of late referrals and non-provision by local hospitals, as opposed to obstetricians at UAH not administering antenatal steroids. There was a statistically significant ($p < 0.05$) difference regarding mortality in neonates where antenatal steroids were not given before preterm delivery in 22 (35.5 %) and the 58 cases that received it (22.8 %) (Table 3).

In a surprising finding, infants receiving surfactant were more likely to demise than those who did not (32.7 % v. 21.7 %, $p=0.0347$). However, considering that pulmonary haemorrhage was the most common cause of mortality in VLBW infants (26.3 %), this statistic places emphasis on the clinical condition of the infants prior to surfactant administration, rather than the administration of surfactant itself.

Pulmonary haemorrhage was most likely attributed to the haemodynamic instability of infants on admission and prior to receiving surfactant. Possible comorbidities, such as patent ductus arteriosus and sepsis, may have placed the infant at increased risk of complications related to the administration of surfactant. Generally, the benefits of surfactant use out-way the risks, but greater awareness of possible complications is highlighted by this study.

Acidosis and hypothermia prior to the administration of surfactant are two factors that may have also increased the probability of developing a pulmonary haemorrhage, and therefore increasing the likelihood of mortality ^[9]. Mortality in patients admitted with hypothermia (temperature less than 36.5°C) was significantly higher than those who were normothermic (30.0 % v. 13.0 %, $p=0.0022$). Certain values reported on admission blood gases were also shown to have an increased risk of mortality. A pH of < 7.1 mmol/L ($p<0.0001$), a base deficit of ≥ 7 mmol/L ($p=0.0003$) and a lactate of ≥ 9.0 mmol/L ($p<0.0001$) all showed this association (Table 4). Addressing admission hypothermia and acidosis as a matter of priority will assist in decreasing the mortality rate in VLBW infants.

Hypoglycaemia, albeit not having shown a statistically significant association with mortality ($p=0.3977$), proved to be a factor which needs to be improved upon at UAH. 114 (42.1 %) patients had an admission glucose of < 2.5 mmol/L, with 84 (26.6 %) having a glucose below 2.0 mmol/L (Table 3). As a preventable factor, hypoglycaemia should be addressed by having a high index of suspicion with clear guidelines or protocols in place to avoid it. All VLBW infants should be screened for hypoglycaemia by point-of-care glucose monitoring as standard practice. Encouraging mothers to express and provide colostrum is highly advisable, should the mother be able to. There should be no delay in establishing intravenous access in these infants and it is advisable to commence total parenteral nutrition as early as possible.

A total of 146 (46.2 %) VLBW infants were intubated (Table 3). Of those intubated, 55 (37.7 %) infants demised. The need for intubation in VLBW infants is an independent risk factor for mortality ($p < 0.0001$). This statistic indirectly reflects the critical condition of these VLBW infants on admission, the haemodynamic instability, the likelihood of needing multiple doses of surfactant, and therefore the increased risk of pulmonary haemorrhages and death.

At UAH, 18.7 % of the study population succumbed to sepsis (Graph 1). This statistic fared better than mortality due to sepsis at CHBH and SBAH, where it accounted for approximately 27.0 % of deaths. ^[1,5]

Limitations of the Study

There are a number of limitations of performing a retrospective study. Patient selection for this study relied solely on admission registries, patient records and the quality of notes formulated. Inaccurate recording or capturing of patient information, as well as capturing of the incorrect patient diagnosis may have had an effect on the data collection process. Incomplete records and failure to record pre-natal and post-natal factors to be reviewed in this study may have potentially impacted this study. Lost records also had a small impact. In a resource-rich setting, with sufficient time and manpower, a prospective study would be recommended. However, in our setting, priority is placed on meeting critical clinical services.

The study results would have greatly benefited from more advanced statistical analysis, such as multivariate logistic regression. This would have provided more clarity regarding the significant association of surfactant administration with increased mortality.

This study was conducted in a central facility. The data may therefore not be reflective of neonatal survival, or mortality, outcomes in secondary level hospitals. A similar study in hospitals delivering different levels of neonatal care should be performed. Comparing mortality and survival rates in VLBW infants of secondary and tertiary level hospitals would help to identify factors contributing to mortality in secondary hospital facilities, which tertiary facilities may be able to address.

Conclusion

Mortality rates, but even more so, survival rates of VLBW infants compare favourably with central hospitals in South Africa and developing countries. Basic interventions, such as improving antenatal care and avoiding neonatal hypothermia, and limiting risk factors associated with pulmonary haemorrhage will minimise the mortality risk. Further studies and investigations would need to be conducted to determine the possible reasons for nearly 20% of preterm deliveries not receiving antenatal steroids. A collaborative effort with obstetric units to emphasise, promote and ensure antenatal steroid provision is of the outmost importance. A focus should be on prompt detection of hypoglycaemia at birth with prompt response in correcting this. Policy change, regarding admission of infants weighing more than 900 grams to intensive care, should be considered to allow escalation of care to improve survival.

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Appendices

- 3.1 APPENDIX A:** Letter of approval from Research Ethics Committee
- 3.2 APPENDIX B:** Permission from DOH
- 3.3 APPENDIX C:** Permission from HOD
- 3.4 APPENDIX D:** Copy of the research protocol approved by the HSREC
- 3.5 APPENDIX E:** Data collection forms, questionnaires
- 3.6 APPENDIX F:** Instructions to authors of the named peer reviewed journal
- 3.7 APPENDIX G:** Turnitin Plagiarism Declaration
- 3.8 APPENDIX H:** Word Count

3.1 APPENDIX A: Letter of approval from Research Ethics Committee



Health Sciences Research Ethics Committee

04-May-2018

Dear Mr Nelson De Abreu

Ethics Clearance: **A Retrospective Analysis of the mortality, and the perinatal risk factors for mortality, of Very Low Birth Weight Infants admitted to Universitas Academic Hospital over a 2 year Period - January 2016 to December 2017**

Principal Investigator: **Mr Nelson De Abreu**
Department: **Paediatrics and Child Health (Bloemfontein Campus)**

APPLICATION APPROVED

Please ensure that you read the whole document.

With reference to your application for ethical clearance with the Faculty of Health Sciences, I am pleased to inform you on behalf of the Health Sciences Research Ethics Committee that you have been granted ethical clearance for your project.

Your ethical clearance number, to be used in all correspondence is: **UFS-HSD2018/0127/2905**

The ethical clearance number is valid for research conducted for one year from issuance. Should you require more time to complete this research, please apply for an extension.

We request that any changes that may take place during the course of your research project be submitted to the HSREC for approval to ensure we are kept up to date with your progress and any ethical implications that may arise. This includes any serious adverse events and/or termination of the study.

A progress report should be submitted within one year of approval, and annually for long term studies. A final report should be submitted at the completion of the study.

The HSREC functions in compliance with, but not limited to, the following documents and guidelines: The SA National Health Act No. 61 of 2003; Ethics in Health Research: Principles, Structures and Processes (2015); SA GCP(2006); Declaration of Helsinki; The Belmont Report; The US Office of Human Research Protections 45 CFR 461 (for non-exempt research with human participants conducted or supported by the US Department of Health and Human Services- (HHS), 21 CFR 50, 21 CFR 56; CIOMS; ICH-GCP-E6 Sections 1-4; The International Conference on Harmonization and Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH Tripartite), Guidelines of the SA Medicines Control Council as well as Laws and Regulations with regard to the Control of Medicines, Constitution of the HSREC of the Faculty of Health Sciences.

For any questions or concerns, please feel free to contact HSREC Administration: 051-4017794/5 or email EthicsFHS@ufs.ac.za.

Thank you for submitting this proposal for ethical clearance and we wish you every success with your research.

Yours Sincerely

Dr. SM Le Grange
Chair : Health Sciences Research Ethics Committee

Health Sciences Research Ethics Committee
Office of the Dean: Health Sciences
T: +27 (0)51 401 7795-7794 | E: ethicsdho@ufs.ac.za
IRB 0006240; REC 230408-011; IORG0065187; FWA00012784



3.2 APPENDIX B: Permission from DOH



health
Department of
Health
FREE STATE PROVINCE

10 April 2018

Mr. NS De Abreu
Dept. of Paediatrics and Child Health
UFS

Dear Mr. NS De Abreu

Subject: A Retrospective Analysis of the mortality, and the perinatal risk factors for mortality, of Very Low Birth Weight Infants admitted to Universitas Academic Hospital over a 2 year Period - January 2016 to December 2017.

- Please ensure that you read the whole document. Permission is hereby granted for the above - mentioned research on the following conditions:
- Serious Adverse events to be reported to the Free State department of health and/ or termination of the study.
- Ascertain that your data collection exercise neither interferes with the day to day running of Universitas Hospital nor the performance of duties by the respondents or health care workers.
- Confidentiality of information will be ensured and please do not obtain information regarding the identity of the participants.
- **Research results and a complete report should be made available to the Free State Department of Health on completion of the study (a hard copy plus a soft copy).**
- Progress report must be presented not later than one year after approval of the project to the Ethics Committee of the University of Free State and to Free State Department of Health.
- Any amendments, extension or other modifications to the protocol or investigators must be submitted to the Ethics Committee of the University of Free State and to Free State Department of Health.
- **Conditions stated in your Ethical Approval letter should be adhered to and a final copy of the Ethics Clearance Certificate should be submitted to sebe@atsa.fshealth.gov.za before you commence with the study**
- No financial liability will be placed on the Free State Department of Health.
- Please discuss your study with the institution manager/CEOs on commencement for logistical arrangements
- Department of Health to be fully indemnified from any harm that participants and staff experiences in the study
- Researchers will be required to enter in to a formal agreement with the Free State department of health regulating and formalizing the research relationship (document will follow)
- You are encouraged to present your study findings/results at the Free State Provincial health research day
- Future research will only be granted permission if correct procedures are followed see <http://ahnd.hst.org.za>

Trust you find the above in order.
Kind regards

Dr D Motau
HEAD: HEALTH
Date: 2018/04/10

3.3 APPENDIX C: Permission from HOD



16 February 2018

Medical Ethics Committee
Faculty of Health Sciences
UFS
BLOEMFONTEIN
9301

Dear Dr Esme Le Grange

APPROVAL: RESEARCH PROJECT - DR N.S. DE ABREU

I hereby certify that this project is being conducted under the auspices of the department of Paediatrics and Child Health, and has our full support.

Permission is hereby granted to collect the data in Neonatology.

Title of project:

"A retrospective analysis of the mortality, and the perinatal risk factors for mortality, of Very Low Birth Weight Infants admitted to Universitas Academic Hospital (UAH) over a 2 year period - January 2016 and December 2017.

Please contact me if there is any questions.

Kind regards

A handwritten signature in black ink that reads 'J. Kriel (acting head)'. The signature is written in a cursive style.

DR J KRIEL
CONSULTANT
DEPARTMENT OF PAEDIATRICS AND CHILD HEALTH

3.4 APPENDIX D: Copy of the research protocol approved by the HSREC

RESEARCH PROTOCOL

A retrospective analysis of the mortality, and the perinatal risk factors for mortality, of very low birth weight Infants admitted to Universitas Academic Hospital over a 2-year period – January 2016 to December 2017

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Summary

A rise in preterm deliveries, especially preterm infants who are born with very low birth weights less than 1500 grams, is currently introducing a global public health dilemma. A rise in preterm deliveries, particularly in a setting such as South Africa, can be attributed to the high incidence of teenage pregnancies, the rise in infants born to mothers of advanced maternal age, but also to the provision of antenatal care with the ability to identify high risk pregnancies in need of premature delivery.

The increase in preterm deliveries, has led to advancements in neonatal medicine and neonatal critical care which have aimed to improve survival in premature infants. Despite these advancements, much needed interventions and equipment, in a setting such as South Africa, are limited. This has contributed to high mortality rates in very low birth weight infants, particularly in the early neonatal period.

This study aims to investigate and determine the mortality rate of very low birth weight infants admitted to the Neonatal Unit at Universitas Academic Hospital, and aims to focus on perinatal factors that confer a risk for a poorer outcome for these infants.

Selected Definitions

Antenatal Care

- The Clinical assessment of the mother and foetus during pregnancy.

Antenatal Steroids

- Medication that is administered to pregnant women in preterm labour, prior to delivery. It has been shown to reduce the morbidity and mortality related to hyaline membrane disease.

Apgar Score

- Scores that are recorded at 1 and 5 minutes after birth that indicate the overall well-being of the new-born.

Early Neonatal Death

- The death of a neonate within the first 7 days of life.

Extremely Low Birth Weight Infants

- Newborns that are born with a weight less than 1000 grams.

Gestational Age

- The duration of the pregnancy. Calculated from the first day of the last normal menstrual period.

High Frequency Oscillatory Ventilation - Unconventional mechanical ventilation

using respiratory rates greater than 4 times the normal value, and very small tidal volumes.

Kangaroo Mother Care

- A way of caring for premature babies through skin-to-skin contact.

Late Neonatal Death

- The death of a neonate after 7 days of life, but before 28 completed days.

Mechanical Ventilation

- The technique through which gas is moved toward and from the lungs through an external device connected directly to the patient.

Nasal Continuous Positive Airway Pressure - A form of positive distending airway

pressure where mild air pressure is applied on a continuous basis to keep the airways continuously open.

Neonatal

- new-born infants up to the age of 28 days.

Neonatal Mortality Rate

- The probability of dying during the first 28 days of life, expressed per 1 000 live births.

Prematurity

- A premature birth is one that occurs before the start of the 37th week of pregnancy.

Surfactant Therapy

- The medical administration of exogenous surfactant with the purpose of lowering the surface tension at the air/liquid interface within the alveoli of the lung.

Very Low Birth Weight Infants

- New-borns that are born with a weight less than 1500 grams. This includes ELBW infants.

List of abbreviations

| | | |
|-----------|---|---|
| C-Section | – | Caesarean Section |
| CHBH | – | Chris Hani Baragwaneth Hospital |
| CMH | – | Charlotte Maxeke Hospital |
| DOH | – | Department of Health |
| E.g. | – | For Example |
| ELBW | – | Extremely Low Birth Weight |
| ENND | – | Early Neonatal Death |
| FS | – | Free State |
| HFOV | – | High Frequency Oscillatory Ventilation |
| HMD | – | Hyaline Membrane Disease |
| I.E. | – | That Is |
| IVH | – | Intraventricular Haemorrhage |
| LNND | – | Late Neonatal Death |
| NCPAP | – | Nasal Continuous Positive Airway Pressure |
| NEC | – | Necrotising Enterocolitis |
| NICU | – | Neonatal Intensive Care Unit |
| NMR | – | Neonatal Mortality Rate |
| NVD | – | Normal Vaginal Delivery |
| RDS | – | Respiratory Distress Syndrome |
| SBAH | – | Steve Biko Academic Hospital |
| SGA | – | Small for Gestational Age |
| NHCU | – | Neonatal High Care Unit |
| UAH | – | Universitas Academic Hospital |
| UFS | – | University of the Free State |
| VLBW | – | Very Low Birth Weight |

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1. Introduction

With the ever-increasing incidence of preterm deliveries and preterm infants born with very low birth weights (VLBW), neonatal centers and health care providers need to be equipped with quantitative evidence so that management and treatment protocols can be drafted using an evidence-based approach.

Within a setting with already limited resources to care for this vulnerable population, information and data regarding mortality, disease profile and perinatal factors contributing to mortality are also limited. Such evidence and insight would allow for health care providers to gain a better insight and understanding into areas that should be addressed to improve survival of VLBW infants, and allow for the motivation of much needed interventions and equipment required to reduce mortality.

Being able to justify rationing of resources and interventions to those infants associated with better outcomes is of the utmost importance in resource-limited settings. The use of precious resources in patients proven to have poor outcomes or where treatment is considered to be futile, which will prolong suffering, goes against the first principal of clinical practice – ‘first do no harm’.

This study will address the problem of limited data regarding mortality in VLBW infants at Universitas Academic Hospital (UAH). By so doing, information and evidence will be provided to better guide neonatal centers in the Free State (FS) Province in reducing mortality rates.

2. Background

2.1. Literature Review

2.1.1. Neonatal Mortality

Globally, there are approximately 130 million babies born every year (1). 15 Million of these infants are born premature, i.e. more than 1 in 10 babies are born premature, with this global statistic rising each year (2). 14% of these births represent those who are born with a VLBW (1). This weight category represents a vulnerable group, with the risk of mortality being reported as being 200 times more likely than those born with a normal birth weight of greater than 2500 grams (3).

Of the worldwide deaths in 2016 among children under the age of 5 years, 46% of these deaths were neonates. 60-80% of these neonatal deaths occurred in those that were born with a VLBW (1). These overwhelming statistics, together with the increase in the South African neonatal mortality rate (NMR) from 11 per 1000 live births in 2013, to that of 12.4 per 1000 live births in 2016, has clearly contributed to the failure of South Africa achieving the target set for the Millennium Development goal, particularly Goal 4, of achieving a two-thirds reduction in childhood mortality by 2015 (4).

The difference in mortality rates of VLBW infants around the world can be differentiated between those seen in developed countries versus those seen in developing countries. Countries such as Thailand and Italy have mortality rates of 19% and 19,6% respectively; India has reported a mortality rate of 33,3% in VLBW infants, with Iran and Jamaica reporting a mortality rate of 50% and 57% respectively (3).

Survival rates of extremely low birth weight (ELBW) infants are far less than those of VLBW infants. In previous studies, survival rates of ELBW infants have shown to be that of 36,6% in Iran, 44% in Italy and 51.8% in the United States, with South Africa achieving survival rates of around 34.9% (3).

In South Africa, similar studies have been performed at Charlotte Maxeke Hospital (CMH) situated in Johannesburg.

A study comparing the morbidity and mortality of VLBW infants over 2 different periods, i.e. 2006/2007 and later in 2013, has shown survival rates of 70,2% and 73.4% respectively (5,6). This is consistent with survival rates of other developing countries. However, limited evidence is available showing the survival rate, and conversely the mortality rate, of VLBW infants in the FS Province and that of UAH.

2.1.2. Disease Profile

The top 4 causes of death in VLBW infants are:

- Immaturity related
 - Hyaline Membrane Disease (HMD)
 - Necrotising Enterocolitis (NEC)
 - Intraventricular Haemorrhage (IVH)
 - Pulmonary Haemorrhage
- Sepsis
- Perinatal Asphyxia
- Congenital Abnormalities

The causes noted above have been consistent with various studies conducted in South Africa. At Chris Hani Baragwanath Hospital (CHBH), immaturity accounted for 63% of deaths (7). At Steve Biko Academic Hospital (SBAH) and CMH, mortality due to immaturity accounted for 43% and 40% of deaths, the top cause of death at both of these institutions (1,5,6). Sepsis accounted for approximately 27% of deaths at both CHBH and SBAH (1,5,6).

2.1.3. Perinatal Risk Factors

Multiple studies have investigated various perinatal risk factors and predictors of mortality. Birth weight and gestational age have been the most studied of these factors, with an inverse relationship between these factors and mortality being demonstrated (3,8).

With decreasing birth weight and gestational age, mortality rates have shown to increase, with the greatest mortality rate being in those infants born with ELBW and a gestational age of less than 32 weeks (3,8).

Scoring systems, such as the Clinical Risk Index for Babies (CRIB II), have used perinatal factors in assisting to predict mortality, particularly in infants with a VLBW (12). This scoring system uses infant birth weight, gender, gestational age, the presence of hypothermia and an arterial blood gas within an hour of admission (12).

Other important factors shown to impact mortality rates include those of maternal age, antenatal care, the infant being small for gestational age, the provision of antenatal steroids and post-natal surfactant administration, mode of delivery, Apgar scores, the presence of chorioamnionitis, maternal illness, nasal continuous positive airway pressure (NCPAP) and mechanical ventilation (5-10).

2.1.3.1. Maternal Age

Those infants born to mothers of both extremes are at increased risk of mortality, i.e. infants of teenage mothers (less than 18 years of age) and those mothers with advanced maternal age (mothers greater than 35 years of age).

2.1.3.2. Antenatal Care

With regular attendance at antenatal clinics and subsequent regular follow-ups, neonatal mortality has shown to decrease (5-7). Antenatal care allows for mothers who are at high risk of preterm labour to be identified early on in their pregnancies. In so doing, early and appropriate referrals to more specialised centres equipped with obstetric services and neonatal intensive care facilities are possible, contributing to a reduction in mortality rates.

2.1.3.3. Maternal condition and illness

Maternal illness has shown to have an impact on neonatal outcome. These conditions include those of maternal hypertension, diabetes, the presence of chorioamnionitis and HIV infection – all of which place new-borns at a higher risk for mortality (5,6).

2.1.3.4. Antenatal Steroids and Post-Natal Surfactant Administration

Respiratory distress syndrome (RDS), otherwise known as HMD, is a common cause of neonatal mortality. This condition is as a result of lung immaturity and surfactant deficiency.

Administration of steroids to a pregnant woman at risk of preterm delivery, and subsequent administration of rescue doses of surfactant, contributes to a lower mortality rate. Early use of surfactant, within the first 2 hours, is associated with a reduction in mortality as compared to the late administration of surfactant (11).

A single course of antenatal steroids given to mothers who are in preterm labour, at a gestation of less than 34 weeks, significantly reduces the incidence of RDS and that of neonatal deaths by 31% (11). Other benefits of using antenatal steroids are the reduction in incidence of IVH by 46%, and a 54% reduction in NEC (11).

2.1.3.5. Mode and Place of delivery

Premature infants born by caesarean section (C-section) have a lower mortality rate compared to those born by normal vaginal delivery (NVD) (5,9). Mortality rates have also shown to be higher in those born before arriving at a medical facility, as opposed to those born at a clinic or hospital. Furthermore, a greater risk of mortality has been noted in patients that were referred in from other institutions (i.e. out born patients) versus those that were born at a tertiary level facility (5,9).

2.1.3.6. Small for gestational age

Newborns born small for gestational age (SGA) are at a greater risk of mortality than those born appropriate for gestational age or large for gestational age (8). Neonates who are below the 10th percentile on the Fenton growth chart are considered to be small for gestational age.

2.1.3.7. Infant Gender

Male newborns have been shown to have a greater risk of mortality compared to female newborns, particularly when born prematurely (7). Male newborns are at increased risk of RDS due to delayed lung maturity as compared to female newborns.

2.1.3.8. Apgar Score

Apgar scores at 1 minute and 5 minutes after birth have been associated with patient outcome. An Apgar score of less than 6 at 5 minutes has been shown to increase the risk of mortality (7,9).

2.1.3.9. Admission Blood Gas

Predictive scoring systems, such as the CRIB II score, have used the base excess value on arterial blood gases performed within an hour of birth, as a predictor of mortality (12). With a more negative base excess value, the greater the risk for mortality has been shown (12).

2.1.3.10. Hypothermia

Hypothermia on admission has been shown to be an independent risk factor for mortality. Mortality rises with the severity of hypothermia (11, 12).

2.1.3.11. NCPAP and Mechanical Ventilation

ELBW infants, who would otherwise not qualify for intubation and mechanical ventilation, have improved outcomes with decreased mortality rates when NCPAP was initiated. In resource limited settings, where only a number of NCPAP machines are available, this is not always a feasible option (6,11).

NCPAP has shown to reduce the need for intubation and mechanical ventilation by 38% and reduce death or respiratory failure by 35% (11).

Other advantages of using NCPAP over invasive mechanical ventilation are that it is simple to use, does not need specialised intubation skill and is non-invasive, which makes it an appropriate mode of respiratory support that can be used outside the neonatal intensive care unit (NICU) (11).

In resource-limited areas and developing countries, the belief that only modern, expensive interventions (i.e. conventional ventilation and high frequency oscillatory ventilation (HFOV)) can improve neonatal outcome is not appropriate (1).

With interventions such as antenatal steroids, NCPAP, and early administration of surfactant, together with in-expensive and cost-effective interventions such as providing Kangaroo mother care, breast milk and the prevention of hypothermia, the expectation for a reduced mortality rate in VLBW infants should be a practical expectation, rather than a goal (1,11).

The focus globally is now to work towards attaining the 2025 Born too Soon goal of achieving a 50% reduction in the under-5 mortality rate (2). Given that prematurity contributes significantly to childhood mortality, the focus should be decreasing preterm deliveries of infants, and to evaluate our current statistics, be it nationally, provincially and even that of individual institutions.

With a focus on neonatal mortality and the factors that contribute to this mortality, we can focus our aim at providing interventions and services towards limiting these factors, and thereby improving survival of this vulnerable group.

2.2. Hospital Facilities and Services

UAH is a tertiary Hospital in Bloemfontein, South Africa, which serves the entire FS Government System. The Academic complex also accepts referrals from the Northern Cape and Lesotho.

The **Obstetric Unit** functions as a high care unit. Pregnant woman with maternal or fetal conditions placing them at high risk are admitted to UAH, where their infants are subsequently delivered. Maternal conditions placing pregnant woman at high risk include those of gestational hypertension, pre-eclampsia and HELLP syndrome, maternal cardiac conditions such as rheumatic heart disease with valvular pathologies, cardiac failure, gestational diabetes and maternal seizures. Pregnant woman admitted to the Obstetric Unit are at times critically ill and represent a different clinical picture compared to those who present at peripheral medical facilities.

Fetal conditions classifying pregnancies at high risk include congenital malformations, Doppler ultrasounds revealing abnormal or absent blood flows, and those pregnancies classified as high risk where the foetus is in distress or extremely premature.

The **Neonatal Unit** consists of three different divisions, and is so divided according to the provision of interventions. These 3 units admit around 600 neonates per year, approximately 250 of whom are very low birth weight infants.

2.2.1. The Neonatal Intensive Care Unit

The NICU is a 14-bed intensive care unit which allows for the provision of ventilation and HFOV. There is a standardised protocol stating that infants born greater than 1000 grams who require intubation will be admitted to the NICU. However, admission to the NICU is on a case by case basis. Infants born less than 1000 grams may be considered for NICU admission and mechanical ventilation depending on the resources and number of staff available. Maternal history, the fetal well-being during labour and the response to new-born resuscitation are also taken into account.

Since the end of 2017, the unit was subdivided into three different cubicles. These cubicles include those providing for medical related patients, pre- and post-surgical patients and an isolation cubicle where patients with proven sepsis are isolated. This has been established in an attempt to decrease the sepsis rate in this unit.

2.2.2. Neonatal High Care Unit (NHCU)

The NHCU has no restrictions for admission, in terms of birth weight. This unit provides a 16-bed minimum; however, this unit has been known to admit as much as 20 patients from time to time. The provision of NCPAP and high flow oxygen is readily available in this unit. Infants born with a weight greater than 800 grams qualify for the provision of these interventions in NHCU.

2.2.3. Neonatal Ward

The Neonatal Ward functions as a transitional unit. Patients admitted here are those patients nearing discharge, those only awaiting maternal discharge from obstetrics, or those simply awaiting review by other specialties. The Neonatal Ward usually accommodates those infants greater than 1200 grams requiring little to no intervention, and this unit usually experiences the greatest turnover.

3. Problem Statement

The problem that will be addressed by this study is that of limited local data pertaining to the mortality of VLBW infants at UAH. By quantifying mortality in this vulnerable population, together with identifying risk factors contributing to mortality, informed decisions can be made. Decisions regarding the provision and rationing of interventions and resources towards those with better outcomes, in a resource-limited setting such as those seen in South Africa, can be made.

4. Aims of the Study

The aim and primary objective of this study is to determine the mortality rate and disease profile of very low birth infants that were born at UAH and subsequently required admission into the Neonatal Unit. This study will focus on those admissions and mortalities that occurred over the 2-year period starting 1st January 2016, and ending 31st December 2017.

5. Objectives

The *primary objective* of this study is to determine the mortality rate and disease profile of very low birth infants born at UAH and subsequently requiring admission into the Neonatal Unit.

The *secondary objectives* of this study will be to collect data and determine the presence of perinatal factors, which literature has shown to have an impact on mortality and survival, in all VLBW infants admitted into the Neonatal Unit.

The factors to be considered are as follows:

- i. Maternal Factors
 - Maternal Age
 - Maternal condition and illness
 - Antenatal Care
 - HIV status
 - Presence of Chorioamnionitis

- ii. Delivery Related factors
 - The provision of antenatal steroids
 - Type of delivery
 - Out born vs. Inborn delivery
 - Born Before Arrival

- iii. Infant Factors
 - Infant Gender
 - Birth Weight
 - Gestational Age and the appropriateness for gestational age (i.e. small, large or appropriate for gestational age)
 - Apgar Scores at 1 minute and 5 minutes
 - Administration of Surfactant
 - Admission blood gas (particularly pH, base excess and lactate)
 - Hypothermia

Finally, as data will be collected on all VLBW infants admitted to the Neonatal Unit, an objective would be to compare the outcomes between those infants born outside of UAH and those delivered at UAH.

6. Methodology

6.1 . Study Design

This study will be a retrospective analytical cross-sectional study primarily consisting of quantitative elements.

6.2 . Study Population

The population of this study will consist of all VLBW infants admitted to the Neonatal Unit. These infants are to be born, and subsequently admitted, into the Neonatal Unit during the period of 1st January 2016 and ending 31st December 2017.

Since records of all VLBW infants born and admitted during the stipulated period are to be reviewed, no sampling method is required.

6.2.1. Sample Size

The estimated sample size for this study is approximately that of 300 VLBW infants.

6.2.2. Inclusion Criteria

- VLBW infants admitted to the Neonatal Unit;
- Admission to all sub-units, namely NICU, NHCU and the Neonatal Ward; and
- All VLBW infants admitted to UAH, regardless of the reason for admission (i.e. surgical or medical pathology).
- Those infants with congenital syndromes and abnormalities.

6.2.3. Exclusion Criteria

- Still births or deaths occurring in the obstetrics unit prior to potential admission to the Neonatal Unit.

7. Measurement

The candidate of this study will obtain details of VLBW infants admitted to the Neonatal Unit from the admission registry from all 3 sub-units, namely those of the NICU, NHCU and the neonatal ward. These registries provide information such as date of birth, date of admission and discharge, and date of demise. The registry also provides the diagnosis and weight of these patients.

For other required details, the candidate of this study will review computerised summaries which are formulated with each patient admission on the internal information system of UAH, Medi-tech. Lastly, patient statistic forms that are completed with each patient admission, documenting the course of each patient's stay, together with patient files will also be used to supplement any information not obtained from Medi-tech.

A pre-designed data capture form (see appendix), formulated and based on the information gathered by the literature review, will be used to collect all the information required for this study. This data capture form will be formulated by the candidate of this study.

Once all data is captured on the data capture forms, and transferred onto an Excel Sheet, the Department of Biostatistics will assist with extrapolating statistical data.

8. Ethics

Prior to data collection, approval for this study will be obtained internally from the Health Sciences Research Ethics Committee of the University of the Free State (UFS), and externally from the FS Department of Health (DOH).

Being a retrospective study where patient records will be reviewed; patient consent is not required. The information to be collected will only be collected by the candidate conducting the study who is to assign each patient record with a numerical value, thereby excluding any patient identifying data from each case.

9. Statistics

9.1. Pilot study

A pilot study will be conducted only once approval for the study has been obtained from the Ethics Committee. The first 5 cases to be included in this study will serve as the pilot population where data will be captured on the data capture sheet and subsequently transferred onto an Excel spread sheet. This will assist in identifying shortfalls of the data capture sheet and the Excel format, and by so doing, allow for changes to the data capture sheet prior to commencing the study.

9.2. Data Capturing and Analysis

All the data collected from the data sheet, and subsequently transferred onto an Excel spread sheet, will be sent to the Department of Biostatistics at UFS for analysis. Results will be summarised as categorical variables (i.e. percentages) and numerical variables (i.e. mean, standard deviations or percentiles).

10. Value of this Study

After the study has been completed, the results will be made available to the hospital management of the UAH Complex, the Department of Paediatrics and Child Health at UFS, and the FS DOH.

This study will positively impact the Neonatal Unit, UAH, the FS DOH and most importantly, the parents of these premature infants. The information gathered better informs the unit as to what the causes of death are, thereby focusing interventions in preventing and reducing mortality. It will provide information regarding which interventions should be available in the Neonatal Unit to prevent mortality in this population.

Results from this study will benefit policy drafting by allowing the justification by health practitioners regarding the restriction or provision of interventions in certain weight categories secondary to limitation of resources.

With regards to parents of VLBW and ELBW infants, such a study will allow for appropriate counselling on expectations, in terms of morbidity and mortality, and better prepare parents for the course of their baby's admission in a neonatal unit, and ultimately their prognosis.

11. Limitations of Study

There are a number of limitations of this study design. Patient selection for this study relies on admission registries, patient records and the quality of notes formulated. Inaccurate recording or capturing of patient information, as well as capturing of the incorrect patient diagnosis may have an effect on the data collection process. Incomplete records and failure to record pre-natal and post-natal factors to be reviewed in this study may potentially impact this study.

12. Time Frame

| | |
|--|------------------------------|
| Planning and Protocol, including the Literature Review | December 2017 - January 2018 |
| Ethics Committee Submission | February 2018 |
| Department of Health Submission | March 2018 |
| Pilot Study and Data Collection | May - June 2018 |
| Data and Statistical Analysis | June – July 2018 |
| Report Writing | July – August 2018 |
| Report Submission | September 2018 |

13. Budget

All costs of the study will be for the account of the candidate of this study. Costs involved in this study will be for stationery and printing, where each case recruited in the study will require data capture sheets. Costs for this study have been calculated based on the assumption that approximately 500 patients are to be included in this study (refer to sample size).

| | |
|----------------------------------|-------------------|
| Paper | R 250 – 00 |
| Printing | R 500 – 00 |
| Other Stationary / Miscellaneous | R 150 – 00 |
| TOTAL | R 900 – 00 |

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3.5 APPENDIX E: Data collection forms

| DATA CAPTURE SHEET | | | | |
|-------------------------------|----------------------------|-----------------------|------------------|----------------------|
| Infant File Number | <input type="text"/> | Case Number | | <input type="text"/> |
| Inborn / Out born | <input type="text"/> | Inborn = 0 | Out born = 1 | <input type="text"/> |
| Born Before Arrival | <input type="text"/> | 0 = no | 1 = yes | <input type="text"/> |
| Gender | <input type="text"/> | Female = 0 | Male = 1 | <input type="text"/> |
| Date of Birth | <input type="text"/> | | | |
| Date of Admission | <input type="text"/> | Length of Stay (days) | | <input type="text"/> |
| Date of Discharge/ Demise | <input type="text"/> | ENND = 0 | LNND = 1 | > 28 days = 2 |
| Demise | <input type="text"/> | Demise | no = 0 | yes=1 |
| ICU Admission | <input type="text"/> | 0 = no | 1 = yes | <input type="text"/> |
| Birth Weight | <input type="text"/> g | 0 = 1250 -1499 | 1 = 1000 - 1249 | <input type="text"/> |
| | | 2= 800 - 999 | 3 = <800g | |
| Gestational Age | <input type="text"/> weeks | 0 = > 32 wks. | 1 = 30 - 31 wks. | <input type="text"/> |
| | | 2 = 28 - 39wks | 3 = < 28 wks. | |
| Appropriateness for Gest. age | <input type="text"/> | 0 = SGA | 1 = AGA | 2 = LGA |

| Perinatal Factors | | | | |
|--------------------|-----------------------------------|---|---------------------------------------|---|
| Maternal Age | <input type="text"/> | 0 = < 18 2 = > 35 | 1 = 18 - 35 | <input type="checkbox"/> |
| Antenatal Care | <input type="text"/> | 0 = no | 1 = yes | <input type="checkbox"/> |
| Antenatal Steroids | <input type="text"/> | 0 = no | 1 = yes | <input type="checkbox"/> |
| Mode of delivery | <input type="text"/> | 0 = NVD | 1 = C/S | <input type="checkbox"/> |
| | <input type="text" value="1min"/> | Apgar @ 1 min | | <input type="checkbox"/> |
| Apgar Scores | <input type="text" value="5min"/> | Apgar @ 5 min | | <input type="checkbox"/> |
| Temp on admission | <input type="text"/> | 0 = > 37.5 2 = 34.5 - 36.0 | 1 = 36.1 - 37.5 3 = < 34.5 | 4 = not recorded <input type="checkbox"/> |
| Arterial Blood Gas | | | | |
| pH | <input type="text"/> | 0 = < 7.0 3 = 7.35 - 7.45 | 1 = 7.0 - 7.19 4 = 7.46 - 7.59 | 2 = 7.2 - 7.34 5 = > 7.6 <input type="checkbox"/> |
| Base Excess | <input type="text"/> | 0 = < -26mmol/L 3 = (-17) - (-11) 6 = > 2 | 1 = (-26) - (-23) 4 = (-10) - (-3) | 2 = (-22) - (-18) 5 = (-2) - 2 <input type="checkbox"/> |
| Lactate | <input type="text"/> | 0 = 0 - 2 3 > 10 | 1 = 2.1 - 5 | 2 = 5.1 - 10 <input type="checkbox"/> |
| Chorioamnionitis | <input type="text"/> | 0 = no | 1 = yes | <input type="checkbox"/> |

Respiratory Support

Intubation

0 = no

1 = yes

CPAP

0 = no

1 = yes

Surfactant

0 = no

1 = yes

HIV exposure

0 = no

1 = yes

Disease Profile

Maternal Condition/ Illness

Infant Diagnosis

Infant Cause of Death



Manuscript preparation

General article format/layout

Submitted manuscripts that are not in the correct format specified in these guidelines will be returned to the author(s) for correction prior to being sent for review, which will delay publication.

General:

- Manuscripts must be written in UK English (this includes spelling).
- The manuscript must be in Microsoft Word or RTF document format. Text must be 1.5 line spaced, in 12-point Times New Roman font, and contain no unnecessary formatting (such as text in boxes). Pages and lines should be numbered consecutively.
- Please make your article concise, even if it is below the word limit.
- Qualifications, *full* affiliation (department, school/faculty, institution, city, country) and contact details of ALL authors must be provided in the manuscript and in the online submission process.
- Abbreviations should be spelt out when first used and thereafter used consistently, e.g. 'intravenous (IV)' or 'Department of Health (DoH)'.
- Scientific measurements must be expressed in SI units except: blood pressure (mmHg) and haemoglobin (g/dL).
- Litres is denoted with an uppercase L e.g. 'mL' for millilitres).
- Units should be preceded by a space (except for % and °C), e.g. '40 kg' and '20 cm' but '50%' and '19°C'.
- Please be sure to insert proper symbols e.g. μ not u for micro, α not a for alpha, β not B for beta, etc.
- Numbers should be written as grouped per thousand-units, i.e. 4 000, 22 160.
- Quotes should be placed in single quotation marks: i.e. The respondent stated: '....'
- Round brackets (parentheses) should be used, as opposed to square brackets, which are reserved for denoting concentrations or insertions in direct quotes.

Preparation notes by article type

Research

Guideline word limit: 3 000 words (excluding abstract and bibliography)

Research articles describe the background, methods, results and conclusions of an original research study. The article should contain the following sections: introduction, methods, results, discussion and conclusion, and should include a structured abstract (see below). The introduction should be concise – no more than three paragraphs – on the background to the research question, and must include references to other relevant published studies that clearly lay out the rationale for conducting the study. Some common reasons for conducting a study are: to fill a gap in the literature, a logical extension of previous work, or to answer an important clinical question. If other papers related to the same study have been published previously, please make sure to refer to them specifically. Describe the study methods in as much detail as possible so that others would be able to replicate the study should they need to. Where appropriate, sample size calculations should be included to demonstrate that the study is not underpowered. Results should describe the study sample as well as the findings from the study itself, but all interpretation of findings must be kept in the discussion section, which should consider primary outcomes first before any secondary or tertiary findings or post-hoc analyses. The conclusion should briefly summarise the main message of the paper and provide recommendations for further study.

- May include up to 6 illustrations or tables.
- A max of 20 – 25 references

Structured abstract

- This should be no more than 250 words, with the following recommended headings:
 - **Background:** why the study is being done and how it relates to other published work.
 - **Objectives:** what the study intends to find out
 - **Methods:** must include study design, number of participants, description of the intervention, primary and secondary outcomes, any specific analyses that were done on the data.
 - **Results:** first sentence must be brief population and sample description; outline the results according to the methods described. Primary outcomes must be described first, even if they are not the most significant findings of the study.
 - **Conclusion:** must be supported by the data, include recommendations for further study/actions.
- Please ensure that the structured abstract is complete, accurate and clear and has been approved by all authors. It should be able to be intelligible to the reader without referral to the main body of the article.
- Do not include any references in the abstracts.

Illustrations/photos/scans

- If illustrations submitted have been published elsewhere, the author(s) should provide evidence of consent to republication obtained from the copyright holder.
- Figures must be numbered in Arabic numerals and referred to in the text e.g. '(Fig. 1)'.
 - Each figure must have a caption/legend: Fig. 1. Description (any abbreviations in full).
 - All images must be of high enough resolution/quality for print.
 - All illustrations (graphs, diagrams, charts, etc.) must be in PDF form.
 - Ensure all graph axes are labelled appropriately, with a heading/description and units (as necessary) indicated. Do not include decimal places if not necessary e.g. 0; 1.0; 2.0; 3.0; 4.0 etc.
- Scans/photos showing a specific feature e.g. *Intermediate magnification micrograph of a low malignant potential (LMP) mucinous ovarian tumour. (H&E stain).* –include an arrow to show the tumour.
- Each image must be attached individually as a 'supplementary file' upon submission (not solely embedded in the accompanying manuscript) and named Fig. 1, Fig. 2, etc.

Tables

- Tables should be constructed carefully and simply for intelligible data representation. Unnecessarily complicated tables are strongly discouraged.
- Large tables will generally not be accepted for publication in their entirety. Please consider shortening and using the text to highlight specific important sections, or offer a large table as an addendum to the publication, but available in full on request from the author.
- Embed/include each table in the manuscript Word file - do not provide separately as supplementary files.
- Number each table in Arabic numerals (Table 1, Table 2, etc.) consecutively as they are referred to in the text.
- Tables must be cell-based (i.e. not constructed with text boxes or tabs) and editable.
- Ensure each table has a concise title and column headings, and include units where necessary.
- Footnotes must be indicated with consecutive use of the following symbols: * † ‡ § ¶ || then ** †† ‡‡ etc.

References

NB: *Only complete, correctly formatted reference lists in Vancouver style will be accepted. If reference manager software is used, the reference list and citations in text are to be unformatted to plain text before submitting.*

- Authors must verify references from original sources.
- Citations should be inserted in the text as superscript numbers between square brackets, e.g. These regulations are endorsed by the World Health Organization, ^[2] and others. ^[3,4-6]
- All references should be listed at the end of the article in numerical order of appearance in the Vancouver style (not alphabetical order).
- Approved abbreviations of journal titles must be used; see the List of Journals in Index Medicus.
- Names and initials of all authors should be given; if there are more than six authors, the first three names should be given followed by et al.
- Volume and issue numbers should be given.
- First and last page, in full, should be given e.g.: 1215-1217 **not** 1215-17.
- Wherever possible, references must be accompanied by a digital object identifier (DOI link). Authors are encouraged to use the DOI lookup service offered by CrossRef:
 - On the Crossref homepage, paste the article title into the 'Metadata search' box.
 - Look for the correct, matching article in the list of results.
 - Click Actions > Cite
 - Alongside 'URL =' copy the URL between { }.
 - Provide as follows, e.g.: <https://doi.org/10.7196/07294.937.98x>

Some examples:

- *Journal references:* Price NC, Jacobs NN, Roberts DA, et al. Importance of asking about glaucoma. *Stat Med* 1998;289(1):350-355. <http://dx.doi.org/10.1000/hgjr.182>
- *Book references:* Jeffcoate N. Principles of Gynaecology. 4th ed. London: Butterworth, 1975:96-101.
- *Chapter/section in a book:* Weinstein L, Swartz MN. Pathogenic Properties of Invading Microorganisms. In: Sodeman WA, Sodeman WA, eds. *Pathologic Physiology: Mechanisms of Disease*. Philadelphia: WB Saunders, 1974:457-472.
- *Internet references:* World Health Organization. The World Health Report 2002 - Reducing Risks, Promoting Healthy Life. Geneva: WHO, 2002. <http://www.who.int/whr/2002> (accessed 16 January 2010).

Submission Preparation Checklist

As part of the submission process, authors are required to check off their submission's compliance with all of the following items, and submissions may be returned to authors that do not adhere to these guidelines.

1. Named authors consent to publication and meet the requirements of authorship as set out by the journal.
2. The submission has not been previously published, nor is it before another journal for consideration.
3. The text complies with the stylistic and bibliographic requirements in **Author Guidelines**.
4. The manuscript is in Microsoft Word or RTF document format. The text is single-spaced, in 12-point Times New Roman font, and contains no unnecessary formatting.
5. Illustrations/figures are high resolution/quality (not compressed) and in an acceptable format (preferably TIFF or PNG). These must be submitted as 'supplementary files' (not in the manuscript).
6. For illustrations/figures or tables that have been published elsewhere, the author has obtained written consent to republication from the copyright holder.
7. Where possible, references are accompanied by a digital object identifier (DOI) and PubMed ID (PMID)/PubMed Central ID (PMCID).
8. An abstract has been included where applicable.
9. The research was approved by a Research Ethics Committee (if applicable)
10. Any conflict of interest (or competing interests) is indicated by the author(s).

3.7 APPENDIX G: Turnitin Plagiarism Declaration

Turnitin Originality Report

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Character count: 38,635
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3.8 APPENDIX H: Word Count

ABSTRACT

| Word Count | | ? | × |
|---|-------|---|-------|
| Statistics: | | | |
| Pages | 1 | | |
| Words | 273 | | |
| Characters (no spaces) | 1 699 | | |
| Characters (with spaces) | 1 967 | | |
| Paragraphs | 6 | | |
| Lines | 30 | | |
| <input checked="" type="checkbox"/> Include textboxes, footnotes and endnotes | | | |
| | | | Close |

CHAPTER 1

| Word Count | | ? | × |
|---|--------|---|-------|
| Statistics: | | | |
| Pages | 10 | | |
| Words | 3 106 | | |
| Characters (no spaces) | 17 057 | | |
| Characters (with spaces) | 20 136 | | |
| Paragraphs | 48 | | |
| Lines | 316 | | |
| <input checked="" type="checkbox"/> Include textboxes, footnotes and endnotes | | | |
| | | | Close |

CHAPTER 2

| Word Count | | ? | × |
|---|--------|---|-------|
| Statistics: | | | |
| Pages | 15 | | |
| Words | 3 452 | | |
| Characters (no spaces) | 17 818 | | |
| Characters (with spaces) | 21 163 | | |
| Paragraphs | 302 | | |
| Lines | 810 | | |
| <input checked="" type="checkbox"/> Include textboxes, footnotes and endnotes | | | |
| | | | Close |