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The neurodevelopmental outcomes of neonatal intensive care unit survivors attending the neonatal follow up clinic at a central academic hospital in Gauteng

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The neurodevelopmental outcomes of Neonatal Intensive Care Unit survivors attending the Neonatal Follow Up Clinic at a central academic hospital in Gauteng.

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Abstract

Background: Neonatology has made astounding advances in intensive care which has improved outcomes and survival of infants with serious medical and surgical conditions (Browne 2011; Khan-D'Angelo et al. 2012; Purdy & Melwak 2012). The long term effects that the NICU environment, as well as varying neonatal morbidities, have on NICU graduates may be detrimental to neurodevelopment (Pineda et al. 2014; Leppert & Allen 2012). Developing countries such as South Africa readily adopt the afore-mentioned advances in neonatal care but fail to provide the adequate follow up that is needed for high risk infants (Ballot et al. 2012).

Aim: To assess the neurodevelopmental outcomes of babies discharged from the Chris Hani Baragwanath Academic Hospital NICU when they attend the neonatal follow up clinic.

Methods: 40 participants were assessed according to corrected age, using the *Bayley Scales of Infant and Toddler Development Third edition.*

Results:

Data from 20 male and 20 female participants were analysed. The mean corrected age at time of assessment was 147 days (±38). The mean cognitive score was 87 (Low average), mean language score was 96 (Average) and mean motor score was 93 (Average). It was found that participants with sepsis during NICU admission were at risk of abnormal cognitive development (P=0.018) at a 5% level of significance. On the language scale, no characteristics were significant at P=0.05. However PDA (P=0.076) and RDS (P=0.057) were found to be risk factors for abnormal language development at a 10% level of significance. Participants born via NVD (P=0.004) and those who experienced anaemia (P=0.038) during NICU admission were found to be at risk of abnormal motor development, at a 5% level of significance. Twenty

one percent of participants had confirmed neurological fallout. Two participants were diagnosed with CP

Conclusion: From the results of this study it is clear that infants who had fewer complications during NICU admission had higher neurodevelopmental scores on the Bayley-III. Infants who had many (or more than four) complications as well as a long duration of stay in NICU were more likely to have lower scores on the Bayley-III assessment. However, the mean Bayley-III scores of the population presented in this study (ranging from low average to average) would suggest that all infants who are discharged from an NICU are at risk for a degree of neurodevelopmental delay.

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Declaration

I declare that this research is my own work. It is being submitted in partial fulfilment of the requirements for the degree of Master of Science in Physiotherapy. It has not been submitted before for any other degree or examination at this or any other university.

Samantha Rosie

_____day of _____2016

List of abbreviations

BW:	Birth weight
CW:	Current weight
RVD exp.:	Retroviral disease exposed
NNJ:	Neonatal jaundice
NEC:	Necrotising enterocolitis
KMC:	Kangaroo Mother Child Care
PDA:	Patent ductus arteriosis
RDS:	Respiratory distress syndrome
CLD:	Chronic lung disease
MAS:	Meconium aspiration syndrome
HMD:	Hyaline membrane disease
NE:	Neonatal encephalopathy
PVL:	Periventricular leukomalacia
IVH:	Intraventricular haemorrhage
CVA:	Neonatal stroke (cerebral vascular accident)
HIE:	Hypoxic ischaemic encephalopathy
PA:	Perinatal asphyxia
T/F:	Blood transfusion
LOS:	Length of stay
Multi. Preg.:	Multiple pregnancy
NVD:	Normal vaginal delivery
IPPV:	Intermittent positive pressure ventilation
NPO_2:	Nasal prongs oxygen
NCPAP:	Nasal continuous positive airway pressure
HFOV:	High frequency oscillatory ventilation
ARV’s:	Antiretrovirals

Presentations

1. Gauteng Association for Infant Mental Health Conference

   Title of presentation:

   The neurodevelopmental outcomes of Neonatal Intensive Care Unit survivors attending the Neonatal Follow Up Clinic at a central academic hospital in Gauteng.

   By Samantha Rosie and Joanne Potterton

   Presented by Samantha Rosie

   31 October 2015

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Chapter 1: **Introduction**

1.1 Background

Over the past four decades, neonatology has made astounding advances in intensive care which has improved outcomes and survival of premature infants and infants with serious medical and surgical conditions (Browne 2011; Khan-D'Angelo et al. 2012; Purdy & Melwak 2012). These infants are termed *high risk.* Most commonly, *high risk* refers to "the likelihood of neurodevelopmental disability, which is a group of interrelated, chronic, non-progressive disorders of the central nervous system caused by injury to or malformation of the developing brain" (Leppert & Allen 2012, pp. 920).

The long term effects that the neonatal intensive care unit (NICU) environment as well as varying neonatal morbidities have on NICU graduates may be detrimental (Pineda et al. 2014; Leppert & Allen 2012). NICU graduates may present later in infancy or childhood with different degrees of developmental delay, or other long term complications. Severity and number of complications can be used to identify infants at high risk for disability (Leppert & Allen 2012). Neonates in an ICU environment are among the most fragile patients that physiotherapists will assess and treat, and detrimental effects can occur with routine medical, physiotherapeutic or nursing procedures (Khan-D'Angelo et al. 2012).

Aly et al. (2010) define developmental delay as the inability of a child to acquire developmental milestones at the expected age, 'age-appropriate' functionality, even after allowing for the broad variation of normality. It may be restricted to one domain or be a global developmental delay. Early identification of infants with developmental delay or disabilities will lead to treatment and interventions, which can lessen the impact on the functioning of the child (Aly et al. 2010).

NICU graduates, who are at risk of poor neurodevelopmental outcomes, should attend comprehensive follow up appointments (Maitre et al. 2013; Hilderman & Harris 2014). Many babies who attend such clinics and do not present with obvious neurological deficits or developmental delay, are often not referred to allied services such as physiotherapy. Many of these cases that appeared in infancy to be normal, present at later ages with subtle disorders such as attention deficit and specific learning disorders. It is therefore important that all NICU graduates attend a follow up clinic and undergo developmental screening as early as possible, where a multidisciplinary approach may be employed to facilitate normal development (Greene et al. 2013). Some deficits such as poor vision, hearing deficits, cerebral palsy, and other significant developmental delay appear earlier and appropriate early intervention can commence (Gücüyener et al. 2006).

In 2014, there were 20 137 live births at Chris Hani Baragwanath Academic Hospital (CHBAH). Of these, 596 were admitted over the year to the 12 bed NICU (Nakwa 2015). At this hospital there is a dedicated Neonatal Follow Up Clinic (NNFUC) that runs once a week. NICU graduates return at six weeks post discharge or earlier where necessary. Also included in this clinic are babies who were admitted at the hospital post-natally, but not admitted to NICU. In 2014, a total of 4535 babies attended the NNFUC, giving an average of 412 babies a month as the clinic is closed at the end of December and the beginning of January.

All allied disciplines provide a service in the NNFUC, including physiotherapy, occupational therapy, speech therapy, audiology and dietetics. There is a high load of patients attending the clinic and unfortunately not all babies receive developmental screening or formal assessment. Developing countries such as South Africa readily adopt the afore-mentioned advances in neonatal care but fail to provide the adequate follow up that is needed for high risk infants. This leads to a significant contrast in the level of care received in

NICU and at follow up clinics which are often poorly resourced (Ballot et al. 2012).

1.2 Research question

What are the neurodevelopmental outcomes of NICU graduates at CHBAH?

1.3 Aim

To assess the neurodevelopmental outcomes of infants discharged from the CHBAH NICU when they attend the NNFUC.

1.4 Objectives

1.4.1 To assess neurodevelopmental outcomes once, between three and seven months corrected age

1.4.2 To measure physical growth since NICU discharge at follow up

1.4.3 To identify associations between neurodevelopmental outcomes and birth history and clinical data

1.5 Significance of the study

It is important to identify high risk infants who could benefit from developmental screening, as well as early intervention where needed. The NNFUC at CHBAH has inadequate staffing, time, clinical space, equipment, and basic amenities. Therefore a streamlined and comprehensive way of developmental screening would be beneficial in view of these limitations. Assessing the neurodevelopmental outcomes of NICU graduates and identifying the most high risk infants, would facilitate the screening of infants in a large and busy clinic.

Chapter 2: **Literature review**

2.1 Neurodevelopment

Foetal and infant brain development is unmatched in complexity and rate, in the rest of life (Bardo 2009; White 2011). From 17 to 20 days gestation, the neural plate and neural tube form. Definition of the gyri and sulci is only complete at 35 weeks gestation (Bardo 2009). Between these two events the other brain structures are forming and neuronal differentiation and migration occurs throughout, as well as synaptic and neurochemical development (Massaro et al. 2006). This neurodevelopment in utero is extremely complex and is dependent on many factors including oxygen and nutrient delivery from maternal circulation. At term, or 40 weeks of gestation, myelination begins (Massaro et al. 2006). It is apparent from this knowledge of foetal brain development, that any interruption or adverse event during this intricate process could cause abnormalities or disruption in neurodevelopment. Extreme preterm birth, exposure to toxins, or an inadequate supply of micronutrients or oxygen are examples of factors that may harm neurodevelopment (Massaro et al. 2006). In an infant's first year of life, its brain volume more than doubles and this time in brain development is as critical as that in utero. Pineda et al. 2013 state that neurodevelopment can be influenced by cerebral injury and altered brain development during this vulnerable time.

2.2.1 The Neonatal Intensive Care Unit

Historically, the neonatal intensive care unit (NICU) was primarily designed for "life-saving". It was a harsh environment, survival of preterm infants was a novelty and so the effects of the environment were overlooked (White 2011). Over the past few decades there have been significant advances in medical treatments and technologies in the NICU leading to increased survival rates of preterm infants and infants with serious medical and surgical complications (Browne 2011; Khan-D'Angelo et al. 2012; Purdy & Melwak 2012).

Unfortunately, along with the greater rate of survival of these 'high risk' infants, comes the adverse effects of their immediate environment and threatening medical comorbidities. It is widely known that preterm and sick infants, in particular those who required neonatal intensive care, have an increased risk of neurodevelopmental disabilities (Leppert & Allen 2012). Complications increase as birth weight and gestational age decrease and these multiple complications or risk factors further increase the risk of neurodevelopmental disability (Leppert & Allen 2012; Pineda et al. 2013).

2.2.2 Defining 'high risk'

Leppert and Allen (2012, p.920) refer to high-risk as the "likelihood of neurodevelopmental disability, which is a group of interrelated, chronic, non-progressive disorders of the central nervous system caused by injury to or malformation of the developing brain". There are many different guidelines to follow when identifying infants who may be termed 'high-risk'. Common complications and risk factors can be grouped according to body structures and functions, namely; pulmonary conditions, neurologic conditions, cardiac conditions, organ dysfunctions and other medical conditions (Khan-D'Angelo et al. 2012). Leppert and Allen's (2012) categories of perinatal risk factors are more extensive and include background characteristics, prenatal and obstetric complications, physical characteristics, condition at birth, neonatal complications, and measures of central nervous system (CNS) structure and function.

2.2.3 NICU environmental stressors

When studying the neurodevelopment of neonates, one cannot ignore the effects of the NICU environment and the impact it may have on developing neonates. It is a well-known fact that neonates in NICU, particularly preterm infants, are very sensitive to touch, lighting changes and noise which have numerous effects on their physiological and neurological states, often compromising respiration (White 2011). Even though the highest priority in an

NICU is to save lives, an increasing amount of literature emphasises the impact that the stressful environment has on developing neonates. The first stressors to be investigated were noise and lighting (White 2011). Following this were many studies investigating pain experiences in the NICU, with subsequent development of methods to measure pain and stress of infants (Gibbins & Stevens 2001; Newnham et al. 2009). Loud noises have been found to cause an increase in autonomic response in neonates potentially leading to bradycardia and hypoxic episodes. It is also agreed that bright lights adversely affect neonates particularly those born before 32 weeks gestational age, as they have thin eyelids and decreased ability to limit the amount of light entering the eyes (Khan-D'Angelo et al. 2012).

Studying a preterm infant's perception of pain is complex. Newnham et al. (2009) have described a lack of concordance between behavioural and physiological responses to pain, particularly at earlier gestational ages. But it is agreed that pain in this population can increase blood pressure, heart rate and intracranial pressure and decrease oxygen saturation (Newnham et al. 2009). Many studies have proposed that the bright and noisy environment adversely affects growth and development especially of the very preterm infant (Pineda et al. 2014). Infants in an NICU are exposed to this stressful environment at a critical time of CNS development and vulnerability, and there is increasing evidence that the repeated stressors have profound effects on several physiological systems, one being the CNS (Newnham et al. 2009).

2.3 The effects of common neonatal morbidies on neurodevelopment

2.3.1 Prematurity and low birth weights

Many complications encountered in an NICU are due to prematurity and low birth weights. There is extensive literature linking prematurity and it's effects to neurobehavioural changes and long-term neurodevelopmental difficulties (Khan-D'Angelo et al. 2012; Pineda et al. 2013). In a literature review by

Jarjour (2015), it was found that extreme preterm (EP) infants (less than 25 weeks gestation) have a very low likelihood of surviving without impairment. The author reviewed 16 articles from a 14 year period, and looked at results from both short- and long-term follow up. The review showed that nearly half of the surviving EP infants had significant neurodevelopmental disabilities at follow up. The most frequently ocurring long-term complication was intelectual disability (Jarjour 2015). Low birth weight (LBW) is defined as 1501-2500 grams, very low birth weight (VLBW) is defined as 1000-1500 grams, and extremely low birth weight (ELBW) as less than 1000 grams (Khan-D'Angelo et al. 2012). In a systematic review by Tchamo et al. (2016) it was shown that VLBW and ELBW had a significant association with poor growth and neurodevelopment delay in African children between the ages of zero and five years old.

2.3.2 Chronic lung disease

Chronic lung disease (CLD) and bronchopulmonary displasia (BPD) are two of the most common respiratory complications of preterm birth and are caused by incomplete or abnormal repair of lung tissue during the neonatal period (Khan-D'Angelo et al. 2012; Pfister & Goldsmith 2010; Poon et al. 2013). Embryologically, the lungs develop in five different stages, namely; embryonic, pseudoglandular, canalicular, saccular, and alveolar. Infants that are born at less than 28 weeks gestation have inefficient gas exchange and are at risk of disrupted or arrested alveolarisation as they are only at the late canalicular or early saccular stage (Bhakta & Stark 2006; Poon et al. 2013). Infants with CLD or BPD require supplemental oxygen and often require continued oxygen supplementaion after discharge from hospital in the form of 'home oxygen' (Khan-D'Angelo et al. 2012). Long-term consequences of CLD have been seen in childhood and through to adulthood (Poon et al. 2013). This group of infants generally have poorer neurodevelopmental outcomes compared to unaffected infants. The influence of CLD on development may be associated with poor nutrition and growth (due to increased work of breathing and increased energy requirements), feeding difficulties (due to

oromotor dysfunction), prolonged hospitalisation and repeated nosocomial infections (Bhakta & Stark 2006; Khan-D'Angelo et al. 2012).

2.3.3 Periventricular leukomalacia and intraventricular haemorrhage

Among the many difficulties that preterm infants encounter, cerebral injury is a common morbidity and both cerebral injury and altered cerebral development can negatively influence neurodevelopment in these infants (Pineda et al. 2013; Vollmer et al. 2006). Cerebral injuries are often associated with suboptimal or abnormal neurodevelopmental outcome (Leijser et al. 2009). In particular, preterm infants are at risk of intraventricular haemorrhage (IVH) and periventricular haemorrhage (PVH), periventricular leukomalacia (PVL) and more diffuse white matter injury. Khan-D'Angelo et al. (2012) define PVL as a symmetrical, non-haemorrhagic usually bilateral lesion caused by ischaemia from alterations in arterial circulation. Leijser et al. (2009) refer to PVL as the predominant form of brain injury and the leading known cause of cerebral palsy (CP) in preterm infants. There are many different factors that may cause the change in arterial circulation. It has been shown that lesions which form cysts are correlated with CP and cognitive impairment, where larger and bilateral cysts present a higher risk (De Vries et al. 2004; Khan-D'Angelo et al. 2012).

PVL is often associated with IVH (Volpe 2001). Like various other risk factors, there is an inverse relationship between gestational age and IVH. Haemorrhage occurs from the primitive capillaries, and interferences with cerebral blood flow autoregulation increase the risk of vessel rupture. These disturbances can be caused by any neonatal event that may lead to change in cerebral blood flow, hypoxia or hypoxaemia. IVH can be classified from grades one to four, with grade four being the most severe (haemorrhage into the periventricular white matter). There is a greater incidence of neurodevelopmental problems in infants with severe haemorrhage ranging from CP and hydrocephalus to cognitive, sensory and learning disorders (Khan-D'Angelo et al. 2012).

2.3.4 Necrotising enterocolitis

Necrotising enterocolitis (NEC) is an acute inflammatory disease of the premature infant's bowel (Khan-D'Angelo et al. 2012). Several factors predispose infants to NEC. It can be further classified into medical NEC and surgical NEC (Martin et al. 2010). The relationship between NEC and neurodevelopment is complex. NEC is not seen as the direct cause of poor neurodevelopment. In a study by Martin et al. (2010) they observed that increased severity of disease, i.e. surgical NEC, predisposed infants to adverse neurodevelopment. They explained that the injured gut contributes to a systemic inflammatory response which can affect the developing brain, and that NEC could be a marker for overall severity of illness during the NICU stay. NEC will also expose the infant to other risk factors, for example, anaesthesia during surgery. The study included 1155 infants and assessed neurodevelopment at 24 months corrected age using the Bayley Scales of Infant Development-Second edition (BSID-II). The authors concluded that infants who had surgical NEC were at higher risk for poor developmental outcomes compared to those who didn't (Martin et al. 2010). The risk of adverse neurodevelopment in infants with NEC has also been demonstrated in data collection done by allied health professionals at Chris Hani Baragwanath Hospital (CHBAH) in 2013. The third most common co-morbidity in the population was NEC, and it was associated with motor and cognitive delays (Bulmer 2014).

2.3.5 Neonatal jaundice

In the same data collected at CHBAH, neonatal jaundice (NNJ) was also found to be a co-morbidity in infants with suboptimal development in motor, communication and sensory domains. It was the most frequently occurring risk factor in the population (Bulmer 2014). NNJ or neonatal hyperbilirubinaemia, is defined as the accumulation of excessive amounts of bilirubin in the blood. It is a condition seen in both preterm and term neonates and has numerous causes. Hyperbilirubinaemia becomes dangerous to the

developing brain if unconjugated bilirubin is deposited in the brain, known as kernicterus (Khan-D'Angelo et al. 2012). The part of the brain most affected by unconjugated bilirubin is the basal ganglia. In a small study by Gkoltsiou et al. (2008) seven out of eleven infants of varying gestational age, at risk of kernicterus as neonates, were diagnosed with CP. Three of the seven infants with CP had dyskinetic or athetoid movements and four infants were severely dyskinetic. Despite the small sample size of 11, the study showed that 63.6% of the sample had severe neurological fallout. Mukhopadhyay et al. (2010, p. 333) re-iterate in their study that "the association between a high bilirubin level and brain damage is well-established". Therefore early and effective treatment of NNJ is paramount in preventing kernicterus and subsequent adverse neurodevelopment.

2.3.6 Neonatal sepsis

Neonates are at risk of multiple infections during hospitalisation (Mitha et al. 2013). Sepsis may harm the developing brain and lead to neurological complications such as PVL and ultimately poor neurodevelopmental outcomes (Schlapbach et al. 2011). In a large, well-conducted cohort study on extremely preterm infants, Schlapbach et al. (2011) showed that sepsis independently increased the risk for adverse neurodevelopment. In this study, 541 participants were included and neurodevelopmental assessments were carried out using the BSID-II at 24 months corrected age. Infants with infection were compared to uninfected infants. Ten percent of infants with proven sepsis were diagnosed with CP. In a very large cohort study conducted by Mitha et al. (2013) it was found that infections in preterm infants were associated with a higher risk of CP, compared to uninfected infants. The study included 2277 infants with various confirmed pathogens and assessed long-term neurodevelopment at five years. The frequency of CP was nine percent and that of intellectual impairment was 12%. They found this result to be consistent with the neurotoxic effects of infectious or inflammatory mediators on cerebral white matter (Mitha et al. 2013). In contrast to the

study by Schlapbach et al. (2011), this study did not account for other comorbidities that might have been experienced.

2.4 Term graduates

Historically, there is little literature discussing full-term NICU graduates, particularly their long-term neurodevelopment. However, a significant number are admitted to NICU's. Term infants may not attend a follow up service regularly, as they may not have had the plethora of complications that a preterm infant might have had, yet their conditions are also grave enough to warrant NICU admission. Late-preterm (33-36 weeks gestation) and early-term (37-39 weeks gestation) infants are two additional groups that are not given as much attention as extreme preterm infants. Recent literature has highlighted sub-optimal long-term developmental outcomes in these two groups of neonates (Romeo et al. 2010; Dong et al. 2012).

Term infants are commonly admitted to the NICU for perinatal asphyxia, birth trauma, congenital syndromes, congenital pneumonia, or sepsis (Schiariti et al. 2008). Although they have a greater weight and, for the most part, fully developed body systems, term infants are still at risk of being affected by the adversities encountered in the NICU.

2.5 Follow up and early intervention

Literature suggests that all high-risk infants should attend a comprehensive follow up programme to provide interventions early on (Hilderman & Harris 2014). During follow up at a medical centre, a multidisciplinary team can identify problems or concerns, either medical or neurodevelopmental (Greene et al. 2013). It is the ideal setting for early intervention. Early intervention aims to improve functional outcomes by screening a high-risk population and coordinating therapeutic services (Litt & Perrin 2014). It spans many areas of therapy and is a broad term used to describe the timely assessment and

treatment of individuals with or at risk of any kind of disability, at any age. In this case, early intervention for the purpose of developmental screening of high-risk infants, can be termed 'early childhood intervention' (ECI). The definition used for ECI in infants at risk for developmental disabilities, as quoted by Shonkoff and Meisels in Blauw-Hospers and Hadders-Algra (2005, p. 421) is as follows; "Early Intervention consists of multidisciplinary services provided to children from birth to five years of age to promote child health and well-being, enhance emerging competencies, minimize developmental delays, remediate existing or emerging disabilities, prevent functional deterioration, and promote adaptive parenting and overall family functioning. These goals are accomplished by individualized developmental, educational, and therapeutic services for children provided in conjunction with mutually planned support for their families".

The age at which to begin ECI in this population is debatable, and largely depends on the condition of the child, whether a developmental disorder is already apparent or not yet clear. Different interventions may start as early as in the NICU, post-NICU discharge up to nine months, and from nine months to 18 months as reported in a systematic review of 34 studies by Blauw-Hospers & Hadders-Algra (2005). The evidence for the preferred initiation period is inconclusive, but benefits are reported for all stages. There is also no conclusive evidence as to which physiotherapy techniques are preferred but it is widely suggested that programs be individualised according to a child's age, needs and abilities (Blauw-Hospers & Hadders-Algra 2005; Fernandez et al. 2012; Spittle et al. 2012).

Primarily, the physiotherapist's focus in ECI is motor function however, all disciplines of therapists are encouraged to assess and integrate all facets of a child's development (Hilderman & Harris 2014). This includes considering a child's environment, family and socio-economic situation. Possibly the most important part of ECI is parent or caregiver education and empowerment, in order to facilitate carry-over of skills into daily life (Vanderveen et al. 2009).

In 2012, a Cochrane review was done by Spittle et al. (2012) with the aim of reviewing the effectiveness of early developmental intervention on motor and cognitive development. Twenty-one randomised or quasi-randomised controlled trials involving 3133 infants were included. The studies compared effects of early developmental intervention programmes post-hospital discharge, to standard medical follow up. All infants had gestational ages of less than 37 weeks. Results of the effects on motor and cognitive development were analysed in age groups, namely; infancy (zero to two years), pre-school age (three to less than five years), school ages (five to 17 years) and adulthood. The analysis demonstrated that early developmental intervention had a significant positive effect on cognitive development at infancy and pre-school age, and a small effect on motor development only at infant age. No substantial long-term outcomes were shown in this review (Spittle et al. 2012). The interventions that were included were not able to prevent cerebral palsy or other neuro-motor impairments in a number of infants, but may have an effect on the functional outcomes of the disorders (Hilderman & Harris 2014).

2.6 Neurodevelopment in a developing country

There are a great many factors that influence a healthy infant's neurodevelopment in low- and middle-income countries worldwide. It is estimated that nearly 200 million children do not reach their developmental potential (Sabanathan et al. 2015). When assessing the neurodevelopment of healthy or at-risk infants in a country such as South Africa, it is important to consider the factors that may influence developmental potential. Poverty, infectious diseases, and malnutrition including maternal malnutrition have been found to have long-term detrimental effects on infant development (Kerac et al. 2014; Sabanathan et al. 2015) . Low maternal education level and parental stress due to low socio-economic status may lead to inadequate cognitive stimulation of infants in the household (Wehby & McCarthy 2013). Koutra et al. (2013) conducted a large cohort study which used self-reported

measures by mothers and neurodevelopmental assessments of their infants at 18 months using The Bayley Scales of Infant and Toddler Development-Third edition (Bayley-III). The authors found that maternal post-partum stress and depression may have negative effects on maternal involvement with the infant, putting the infant at risk of delayed cognitive development. Studies have shown that parent-infant interactions may be compromised in families whose infants are NICU survivors, due to the prolonged parent-infant separation and perceived 'caregiving from a distance' as well as parental emotional stress (Vanderveen et al. 2009).

2.7 Human Immunodeficiency Virus

In 2002, prevention of mother-to-child transmission (PMTCT) was initiated in South Africa to reduce the risk of vertical transmission of the human immunodeficiency virus (HIV) from infected mothers to their infants (Coetzee et al. 2005; Sprague et al. 2011) . The progress made in PMTCT programmes has led to the virtual elimination of paediatric HIV in Europe and the United States (Ciaranello et al. 2012). In certain areas in South Africa, breast feeding by HIV infected mothers is still encouraged for adequate infant nutrition, despite the risk of transmission of the virus through breast milk (Hazemba et al. 2016). Even so, rates of mother-to-child transmission are between one and five percent, reaching the goal for 2015 set by the Joint United Nations programme on HIV/AIDS (Ciaranello et al. 2012; Ghanotakis et al. 2012).

HIV has been shown to have an adverse effect on paediatric neurodevelopment, particularly in infants who are not on highly-active antiretroviral therapy (HAART) (Hilburn et al. 2011; Potterton et al. 2010; Whitehead et al. 2013). In the vertical transmission of HIV, infection may occur in an infant's central nervous system during its early development (Hilburn et al. 2011). A study by Whitehead, Potterton and Coovadia (2013) compared the neurodevelopment of 27 HIV-infected infants and 29 HIV-exposed and uninfected infants. The results showed that HIV-infected infants

scored lower on all scales of the Bayley Scales of Infant and Toddler Development Third edition (Bayley-III) compared to HIV-exposed and uninfected infants. These differences were seen from as young as four months of age.

There is little literature on the effects of maternal antiretroviral therapy (ART) on the developing foetal CNS. A large cohort study of 1869 births by Watts et al. (2013) showed that exposure to protease inhibitor-based combination ART in the first trimester was associated with preterm birth and spontaneous preterm birth. Of course, it is accepted that preterm birth may occur in this population due to many other factors including advanced disease, immune response and inflammatory mediators (Watts et al. 2013).

2.8.1 The Bayley Scales of Infant and Toddler Development

When assessing an infant's development there are many standardised assessment tools available, many of which are not validated for use in under-resourced settings in a developing country. The most widely used standardised and norm-referenced tool is the Bayley Scales of Infant Development (BSID) (Whitehead et al. 2014). It is a set of developmental scales designed to measure developmental functioning (Lennon et al. 2008). Nancy Bayley released the first commercially available version of the BSID in 1969 (Lennon et al. 2008). In 1993, the second edition (BSID-II) was published, and the third edition, differently named the *Bayley Scales of Infant and Toddler Development* (Bayley-III) was published in 2006 (Lennon et al. 2008; Piñon 2010).

The Bayley-III now includes a language scale together with the cognitive and motor scales, as well as subscales comprised of receptive language and expressive language, and fine motor and gross motor subscales (Greene et al. 2013). The normative data are representative of the infant population in the USA, between the ages of one month and 42 months. This sample was

stratified on demographic variables that include geographic location, age, sex, and parent education level (Greene et al. 2013; Piñon 2010). In contrast to the previous Bayley scales, the Bayley-III normative data includes infants with various developmental conditions or risk factors. These special groups make up approximately ten percent of the normative data, and include children with cerebral palsy and children with Down syndrome, as well as various neonatal risk factors such as birth asphyxia and prematurity (Crais 2010; Lennon et al. 2008; Piñon 2010). The Bayley-III is found to be both reliable and valid. Inter-rater reliability, test-retest reliability, and internal consistency were examined for reliability. Internal consistency of subscales and relationship with other outcome measures were evaluated for validity (Greene et al. 2013; Piñon 2010)

2.8.2 The Bayley-III Cognitive Scale

This first scale comprises 91 items which are aligned with recent developmental research on cognitive functioning (Armstrong & Agazzi 2010). Items assessing attention, habituation, memory, and conceptual reasoning were added to this scale to address information processing. Problem-solving, processing speed and early play skills were also researched for use in this scale (Armstrong & Agazzi 2010).

2.8.3 The Bayley-III Language Scale

The Bayley-III language scale looks at language and its related skills in the two subscales, receptive and expressive communication. Some areas have been expanded on and include pre-linguistic, social and complex language components (Crais 2010). It is important to note that the term *communication* indicates any means or combination of means that a child may use to interact with another person. This is especially noted in the early development of communication during the pre-linguistic stage, where children use gestures, facial expressions, vocalisations or eye gaze as forms of communication (Crais 2010).

2.8.4 The Bayley-III Motor Scale

The motor scale is divided into fine motor and gross motor subscales. The fine motor subscale evaluates specific skills that look at how effectively a child is able to use their hands to manipulate objects, use tools and play with toys (Case-Smith & Alexander 2010). In particular this subscale assesses early hand and finger movement, reaching and grasping patterns, bimanual coordination, and the functional use of objects (Case-Smith & Alexander 2010).

The gross motor subscale assesses a child's performance of specific gross motor and locomotion tasks that are essential for mobility and play. This scale comprises skills incorporating early movement, postural stability and control, and balance and locomotion (Case-Smith & Alexander 2010). The variability in acquiring motor skills is vast, and many factors need to be considered. Many items in these subscales allow demonstration of a task before it is carried out, therefore considering possible limitations in exposure to a task.

2.9 Conclusion of literature review

A study of the literature shows that infants admitted to an NICU are exposed to many adverse events and due to their fragile nature, immature vital organs and immune systems they are predisposed to many diseases of the new-born and infections. These complications put the infants at risk of disrupted neurodevelopment and many studies presented in this literature review confirm the detrimental effects on long-term neurodevelopment. The need for identification of the infants who are most at risk and the importance of initiating early intervention strategies is highlighted in this review.

Chapter 3: **Methodology**

In this chapter the methodology used to conduct this study will be presented.

3.1 Location and population

The study was conducted at Chris Hani Baragwanath Academic Hospital, Soweto, Gauteng, South Africa. Infants with their caregivers attended the Neonatal Follow Up Clinic (NNFUC) where screening of NICU graduates was performed to identify eligible participants.

3.2 Ethical clearance

Prior to commencing data collection for this study, ethical clearance was obtained from the Committee for Research on Human Subjects of the University of the Witwatersrand (No. M140865 - see appendix 5). Permission was granted by CHBAH to conduct the research in the hospital's NNFUC. Participants were accompanied by one caregiver. Informed written consent was obtained from the caregiver of each participant. There was no need in any case for the informed consent to be translated. All information and records collected from participants and caregivers were used solely for the purpose of this study, and are kept confidential. Privacy of participants was respected in a closed room. Participants who were found to have any neurodevelopmental fallout were referred to appropriate allied disciplines or multidisciplinary clinics.

3.3 Study Design

This is a cross-sectional observational study.

3.4 Inclusion Criteria

Infants who graduated from the NICU at CHBAH.

3.5 Exclusion Criteria

Infants diagnosed with Hypoxic Ischaemic Encephalopathy (HIE) II and HIE III were excluded, as they attend a different follow up clinic.

Infants who were admitted *only* to the Neonatal Theatre unit were excluded as they attend a different follow up clinic. However; infants who underwent a surgical procedure during admission to NICU, remained in NICU, and followed up at the NNFUC were included.

3.6 Study sample

Unit statistics were used to calculate a study sample. In 2012 there were a total of 699 babies admitted to the NICU at CHBAH, giving a mean of 58 babies admitted monthly. Based on a population of 700 babies a year with a confidence interval of 15 and a 95 percent confidence level, a sample of 40 participants was needed for this study. Participants were of similar socio-economic status and cultural backgrounds.

3.7 Measurement tools

Developmental assessment tool: *Bayley Scales of Infant and Toddler Development Third edition* (Bayley-III)

Weight: The *SECA* infant weighing scale

Length: The *SECA* infant measuring board

Head circumference: Standard measuring tape

Clinical data: History sheet

3.8 Procedure

Participants were screened at the NNFUC once a week. If their corrected age was between three and seven months, and they met the inclusion criteria, the caregiver was invited to participate. This was done on a first-come-first-

served basis, caregivers with infants were seated in rows and one row was screened at a time. As soon as a potential participant was identified, the caregiver attending the clinic with the infant was given an information sheet explaining the research study and assessment. If they agreed to their baby participating in the study, they were given a consent form to sign. The participant and caregiver were invited into a separate room where privacy was respected.

This was their regular follow up appointment therefore there were no extra transport costs for caregivers. In the case where infants became agitated or hungry, caregivers were allowed time to console or feed the infants before the assessment was continued. In no case was there a need to re-schedule another assessment owing to adverse infant behaviour.

Participants were assigned study codes (numbers one-40). The developmental assessment was carried out by the primary researcher prior to obtaining the demographic data, so as to minimise bias. The only information known to the researcher while conducting the assessment was the participants' corrected age.

A neurodevelopmental assessment was carried out for each participant, using the *Bayley Scales of Infant and Toddler Development* (Bayley-III). The assessment tool was explained to the caregiver beforehand. Each scale, namely cognition, language and motor, was administered to participants. In cases where participants were born preterm, the participant's age was corrected using 40 weeks gestation as the full-term reference. Standard scores are derived by referring to the norms table appropriate for the adjusted age (Lennon et al. 2008). The researcher conducted all the assessments and has been trained in the use of the Bayley-III. The results for each scale were recorded on the outcomes form. Raw scores obtained from each participant were converted to scaled scores, and scaled scores for each domain were converted to composite scores.

All birth history, demographic and clinical data were collected from the participants' hospital file and recorded on the history form, once the neurodevelopmental assessment was complete.

Weight was measured by the clinic nurse on arrival at the clinic, and obtained from the hospital file by the researcher. Length and head circumference were measured by the researcher, after the neurodevelopmental assessment was complete, and recorded on the history form. All data and scores were later captured on a spreadsheet by the researcher.

All participant information was kept in a filing system and kept confidential.

3.9 Statistical Analysis

Descriptive statistics e.g. mean and standard deviations (SD) were used to describe the demographic characteristics of the population. Percentages were used to summarise the medical histories of the participants.

The scores from the Bayley-III are presented as means and standard deviations.

Non-parametric tests such as the Chi-squared test were used to determine whether there are any relationships between demographic and clinical data and the Bayley-III composite scores. This was done by a statistician.

Scores of the Bayley-III are interpreted as follows (Bayley, 2006):

Qualitative descriptions of composite scores from each domain

130 and above	Very Superior
120-129	Superior

110-119	High Average
90-109	Average
80-89	Low average
70-79	Borderline
69 and below	Extremely low

The results obtained in this study will be presented in chapter four.

Chapter 4: **Results**

The data from 40 participants were analysed.

No participants were excluded from the study. Once data from 40 participants had been obtained, screening was discontinued. One caregiver refused consent.

4.1 Demographic data

The demographic data of the 40 participants is described in table 4.1. It is presented as means and standard deviations.

Table 4.1: Demographic data

Variable	**Mean (SD)**
Gestational age (weeks)	34 (5)
Corrected age (days)	147 (38)
Birth weight (grams)	2056 (852)
Current weight (grams)	6171 (1424)
Current length (cm)	60 (4)
Head circumference (cm)	40 (3)
Maternal age (years)	28 (7)
Apgar 1minute	6 (3)
Apgar 5 minute	8 (2)
Length of ICU stay (days)	20 (26)
Length of O2 dependence (days)	42 (52)

The lowest birth weight among participants was 810 grams and the lowest gestational age was 26 weeks. Table 4.1 illustrates that the mean length of stay in NICU was 20 days, the longest stay in NICU was 135 days, or four months and 15 days. Length of oxygen dependency surpassed NICU stay, with a mean of 42 days and the participant who had the longest duration of oxygen dependency required supplemental oxygen for 244 days (eight

months and four days). This was the participant's age at the time of the assessment. The participant was one of two who were oxygen dependent at the time of assessment. They wore nasal cannulae connected to oxygen tanks. The mean corrected age of participants at the time of assessment was 147 days, or four months and 27 days.

Z-scores were calculated for all participants using weight-for-age and length-for-age. This was done using the corrected age of each participant. Five participants (12.5%) had a Z-score of below minus 3 for weight, and nine participants (22.5%) had a Z-score of below minus 3 for length.

Table 4.2 presents demographic data of the participants that cannot be presented as means, but as frequencies.

Table 4.2: Demographic data as percentage

Variable	**Percentage (%)**
Male	50.0
Female	50.0
Caesarean section	52.5
NVD	47.5
Mother ARV's	32.5
Mother alcohol	2.5
Mother steroids	2.5

There were an equal number of male and female participants. The number of participants born by normal vaginal delivery (NVD) and caesarean section were almost equal with a difference of two participants. All 40 participants were of the same ethnicity (black). One participant's mother drank alcohol during the pregnancy, one mother was given steroids prior to delivery, and 13 mothers were taking ARV's during the pregnancy.

Table 4.3 describes the types of ventilation or oxygen delivery that participants required during their NICU admission.

Table 4.3: Modes of ventilation

Ventilation	Percentage (%)
IPPV	90.0
NPO_2	72.5
NCPAP	57.5
HFOV	10.0

All 40 participants required one or more forms of ventilation. The most frequent type of ventilation used was intermittent positive pressure ventilation (IPPV) with 36 participants (90%) requiring this. Only 10% of participants were put onto high frequency oscillatory ventilation (HFOV). Nasal prongs oxygen (NPO_2) delivered via cannula, and nasal continuous positive airway pressure (NCPAP) were used in 72.5% and 57.5% of participants respectively; a large proportion.

4.2 Medical complications during admission

Table 4.4 documents the variety of conditions that the participants presented with in the study. They are tabulated according to percentage of the population affected.

Table 4.4: Conditions as percentage

Condition	%	Condition	%
Sepsis	67.5	Periventricular Leukomalacia	20.0
Blood transfusion	55.0	Meconium Aspiration Syndrome	15.0
Neonatal Jaundice	37.5	Multiple pregnancy	12.5
Hyaline Membrane Disease	37.5	Hypotension	12.5
Retroviral Disease exposed	32.5	Hyperglycaemia	10.0
Chronic Lung Disease	30.0	Seizures	10.0
Anaemia	30.0	Surgical NEC	7.5
Patent Ductus Arteriosis	27.5	Hypoxic Ischaemic Encephalopathy I	7.5
Necrotising Enterocolitis	25.0	Thrombocytopaenia	5.0
Intraventricular Haemorrhage	22.5	Retinopathy of Prematurity	5.0
Respiratory Distress Syndrome	22.5	Retroviral Disease positive	2.5
Pneumonia	20.0	Neonatal Encephalopathy	2.5

All participants had one or more of the complications listed in table 4.4. The highest number of comorbidities experienced by a single participant during NICU admission was 12. The number of comorbidities decreased with increasing birth weight. IVH and NEC were associated with preterm birth less than 32 weeks gestation. The multiple pregnancies were all twin births and only one twin from each set was admitted to NICU and therefore assessed in the study. All twin pregnancies were associated with preterm birth of less than 34 weeks gestational age.

The table shows that 13 participants (32.5%) were exposed to HIV (retroviral disease exposed). All 13 mothers of these participants were taking ARV's or initiated ARV's during their pregnancy. All 13 participants were given Nevirapine for 6 weeks post-delivery. Only one participant tested positive for HIV.

4.3 Medical complications - specific

4.3.1 Genetic conditions

Genetic conditions or malformations were diagnosed in six participants (12.5%). These included gastroschisis, coanal atresia, micrognathia, cribriform plate haemangioma, unspecified dysmorphism, and mosaic Down syndrome.

4.3.2 Neurological conditions

Neurological conditions were present in nine participants (22.5%). Neurology included seizures, dilated ventricles, cerebral palsy, unspecified hypertonia and jitteriness, arrested hydrocephalus, microcephaly, cerebral infarcts and atrophy, and meningitis.

4.3.3 Surgery during admission

Surgical procedures were performed on nine participants (22.5%). Types of surgery included staged gastroschisis closure, NEC repair, laparotomy and colostomy, PDA closure, pencil drain insertion, diaphragmatic hernia repair, insertion of nasal stents, duodenal atresia repair, cardiac surgery for ventriculo-septal defect, coanoplasty. Two participants underwent more than one surgical procedure.

4.4 Pathogens found in septic participants

Episodes of sepsis occurred in 27 participants (67.5%) during NICU admission. The following table, table 4.5, describes the types of pathogens that were discovered on blood test cultures and the percentage of participants that they occurred in. In some instances, participants were diagnosed with more than one pathogen during admission.

Table 4.5: Pathogens as percentage

Pathogen	Percentage (%)
Unspecified sepsis	25.0
Methicillin-resistant Staphylococcus Aureus (MRSA)	12.5
Acinetobacter Baumanii	12.5
Klebsiella	10.0
Staphylococcus Aureus	7.5
Fungal (unspecified)	7.5
Candida Albicans	7.5
Enterobacter cloacae	2.5
Tropicalis	2.5
Escherichia coli	2.5
Enterococcus faecalis	2.5
Candida parapsilosis	2.5
Group F streptococcus	2.5

Methicillin-resistant staphylococcus aureus (MRSA) and Acinetobacter baumanii are equally the most commonly occurring pathogens in this study population. However, in a quarter of the population, the type of sepsis was not specified.

4.5 Interventions during admission

During NICU admission or post-NICU discharge many neonates undergo non-medical interventions and therapies to promote normal development, increase weight, improve feeding, maintain normal movements and postures, and education of parents. For this population, the different types of non-medical interventions that a portion of participants received are listed in the table below. Participants may have received only one intervention, or all.

Table 4.6: Non-medical interventions as percentage

Intervention	Percentage (%)
Speech Therapy	50.0
Physiotherapy	30.0
Kangaroo mother care (KMC)	5.0

Half of the participants in the study were treated by a speech therapist for difficulty with feeding or assisting with transitioning to oral feeding post-NICU discharge. A lower percentage (30%) of participants were treated by a physiotherapist. This could consist of developmental care or specific rehabilitation exercises, or chest physiotherapy. Only five percent of participants stayed in the KMC unit with their mothers.

4.6 Bayley-III scores

The scores of the neurodevelopmental assessment are presented in means and standard deviations (SD). The composite scores for each scale are presented in the graph and table below.

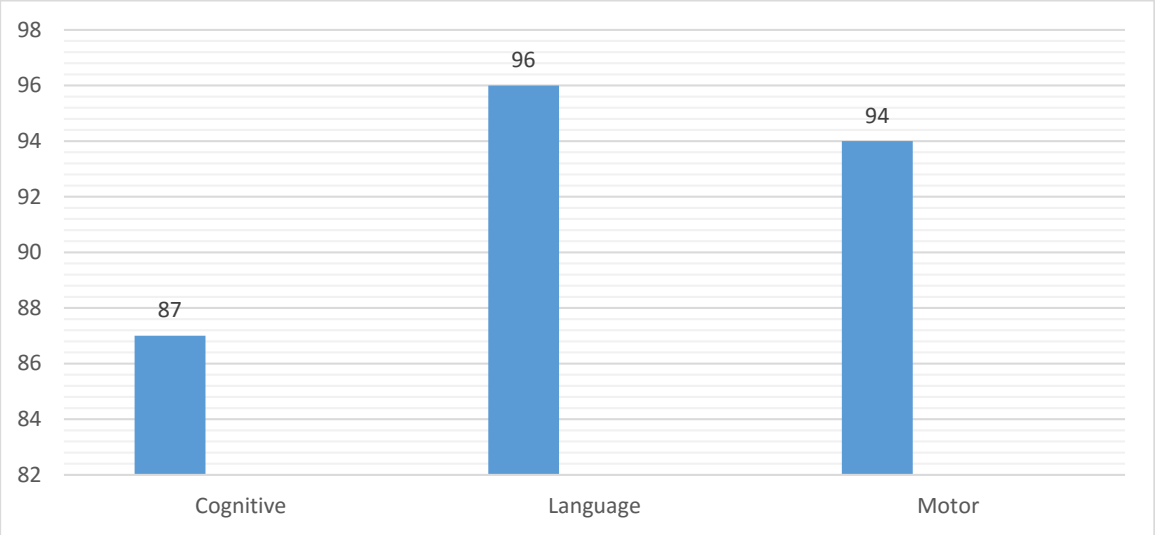


Figure 4.1: Composite scores

This graph illustrates that the cognitive scale has the lowest mean score of 87 (SD=16). The motor scale has a mean score of 94 (SD=11) and the language scale has the highest mean score of 96 (SD=22). All of these scores fall in the average and low average categories.

Table 4.7 presents the highest and lowest composite scores of each scale, namely; cognitive, language and motor.

Table 4.7: Highest and lowest composite scores

Scale	Highest score	Lowest score
Cognitive	120	55
Language	121	77
Motor	145	58

When assessing individual scale composite scores of 40 participants, Table 4.7 confirms that the cognitive scale has the lowest scores, with both the highest and lowest scores being lower than those of the language and motor scales. The motor scale boasts the highest score out of the three scales, however it is not the highest mean score. The lowest cognitive scores were found in participants with respiratory distress syndrome, twin birth, and genetic conditions. The highest motor scores were found in participants with birth weights greater than 3000 grams. The group of females had higher mean scores than the group of males, particularly in the cognitive scale.

The following figures are pie charts representative of each Bayley-III scale. Scoring categories are presented as percentages of the total and are colour-coded according to the key.

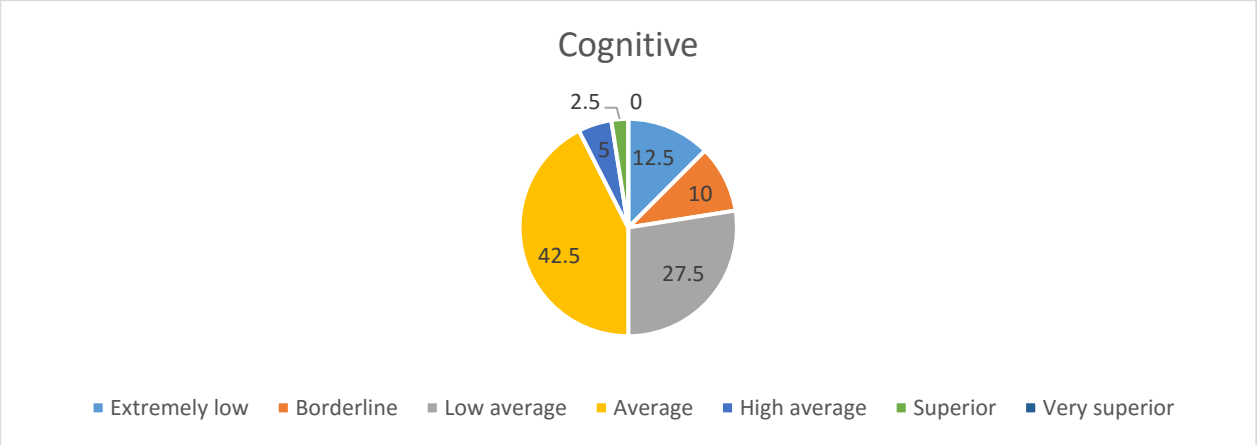


Figure 4.2: Cognitive descriptive groups

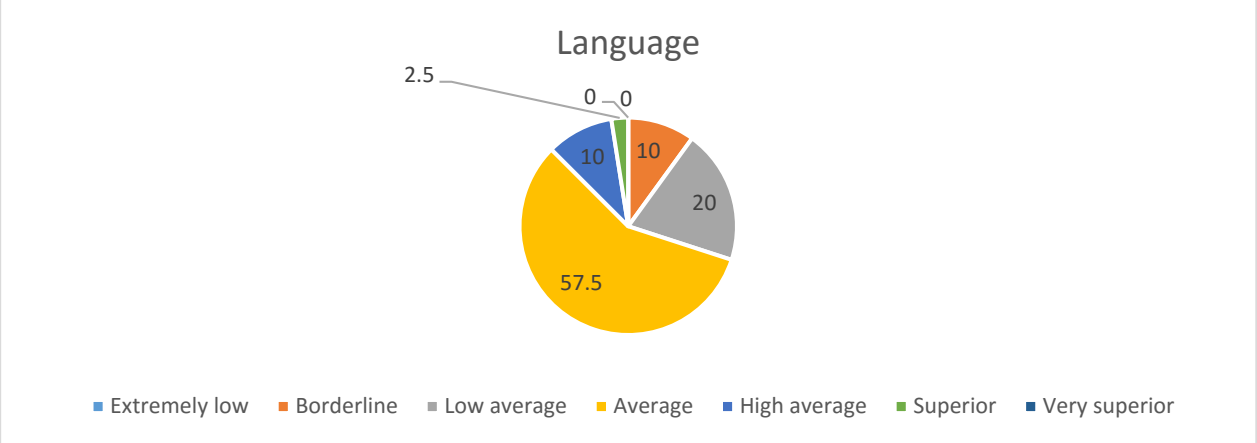


Figure 4.3: Language descriptive groups

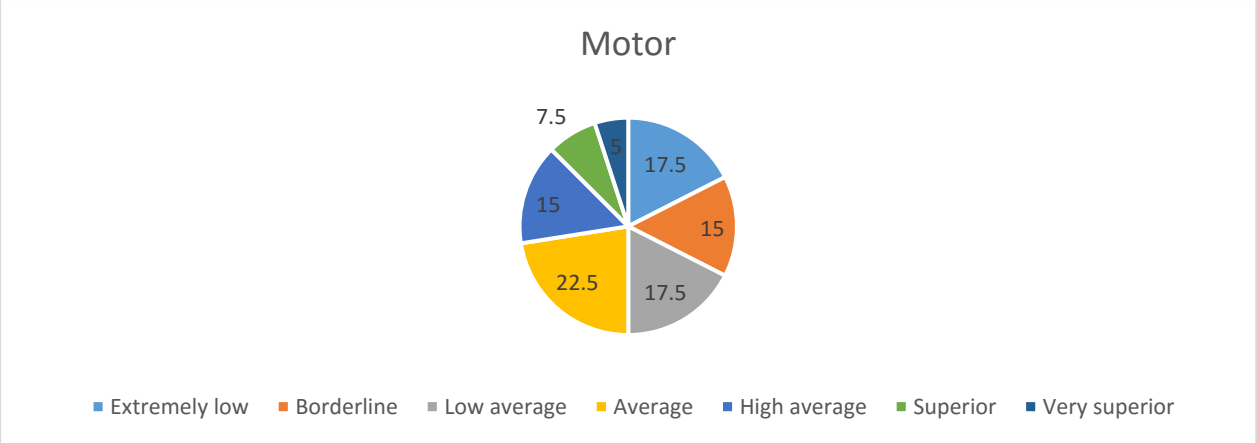


Figure 4.4: Motor descriptive groups

As evidenced by the pie charts, the motor scale has the most widely distributed scores with participants scoring in each category. It is the only scale with very superior participants, making up five percent of the total. The motor scale also has the highest percentage of extremely low scores, being 17.5%.

4.7 Descriptive analysis

Composite scores that were less than or equal to 85 were analysed for each subscale, for each medical complication. The data is presented in table 4.8 as frequencies.

Table 4.8: Frequency of complications in scores ≤85 (at risk) on each scale

Complication	Number on cognitive scale	%	Number on Language scale	%	Number on Motor scale	%
Male	12	60.0	3	15.0	11	55.0
Female	8	40.0	3	15.0	6	30.0
RVD exposed	6	46.1	1	7.6	6	46.1
NVD	12	63.1	4	21.0	12	63.1
Caesarian	8	38.0	2	9.5	5	23.8
IPPV	17	47.2	5	13.8	15	41.6
HFOV	1	25.0	0	0.0	1	25.0
CPAP	11	47.8	5	21.7	10	43.4
NPO2	16	55.1	5	17.2	12	41.3
PDA	5	45.4	0	0.0	3	27.2
CLD	8	66.6	3	25.0	7	58.3
PVL	4	50.0	1	12.5	3	37.5
Sepsis	17	62.9	5	18.5	14	51.8
Twins	4	80.0	1	20.0	4	80.0

NNJ	8	53.3	3	20.0	10	66.6
NEC	6	60.0	2	20.0	7	70.0
NEC surgery	1	33.3	1	33.3	2	66.6
RDS	6	66.6	2	22.2	4	44.4
HMD	8	53.3	2	13.3	8	53.3
MAS	1	16.6	2	33.3	1	16.6
IVH	7	77.7	2	22.2	6	66.6
HIE I	1	33.3	0	0.0	1	33.3
T/F	13	59.0	4	18.1	11	50.0
Seizures	3	75.0	1	25.0	1	25.0
Anaemia	6	50.0	2	16.6	8	66.6
Hypotension	2	40.0	0	0.0	1	20.0
Hyperglycaemia	1	25.0	0	0.0	2	50.0
Thrombocytopaenia	1	50.0	0	0.0	1	50.0
Genetic abn.	4	66.6	1	16.6	3	50.0
Pneumonia	2	25.0	0	0.0	0	0.0
ROP	1	50.0	0	0.0	1	50.0
Neurology	6	66.6	1	11.1	3	33.3
Surgery other	5	55.5	2	22.2	5	55.5

The total number of participants in each scale who had scores less than or equal to 85; were 20, six and 17 on the cognitive, language and motor scales respectively. The participants are classified as ‘at risk’ for abnormal development by their low scores. The language scale has by far the lowest number of abnormal scores, corresponding to the information presented in point 4.6. This very low number accounts for the low percentages of complications found on this scale in table 4.8. On all three scales, in this low-scoring category, the mean gestational age was the same: 33 weeks. The mean birth weights were 1830 grams, 2118 grams and 1788 grams for the cognitive, language and motor scales respectively.

The most frequently occurring complication in this category was twin pregnancy, with 80% occurring in both the cognitive and motor scales. On the cognitive scale in this low-scoring category, the presence of IVH and seizures were frequent with 77.7% and 75% respectively. On the motor scale the next most frequently occurring complication was NEC with 70%.

4.8 Statistical analysis

The data collected in this study was analysed with the use of STATA. The Chi-squared test was used to investigate associations between scores indicating risk of abnormal development and participant characteristics and complications. With a 95% confidence interval, 5% as well as 10% levels of significance were used to show relationships and trends. The significant values are presented in table 4.9, table 4.10 and table 4.11.

Table 4.9 Statistically significant values for characteristics in the cognitive scale

Characteristic	P=0.05	P=0.1
Sepsis	P=0.018	
IVH		P=0.058

Table 4.10 Statistically significant values for characteristics in the language scale

Characteristic	P=0.05	P=0.1
PDA		P=0.076
RDS		P=0.057

Table 4.11 Statistically significant values for characteristics in the motor scale

Characteristic	P=0.05	P=0.1
NVD	P=0.004	
Anaemia	P=0.038	

It was found that participants with sepsis during NICU admission were at risk of abnormal cognitive development (P=0.018) at a 5% level of significance. On the language scale, no characteristics were significant at P=0.05. Participants born via NVD (P=0.004) and those who experienced anaemia (P=0.038) during NICU admission were found to be at risk of abnormal motor development, at a 5% level of significance.

At a 10% level of significance, IVH (P=0.058) was associated with a risk of abnormal cognitive development. PDA (P=0.076) and RDS (P=0.057) were found to be risk factors for abnormal language development at a 10% level of significance.

Trends were discovered on the language and motor scales, with characteristics that were almost significant in terms of risk of abnormal neurodevelopment. These include NVD (P=0.112) on the language scale, and NNJ (P=0.102), NEC (P=0.144) and twin pregnancy (P=0.151) on the motor scale.

4.8 Participant profiles

4.8.1 Lowest overall scoring participants

The following two tables show the scores of the lowest scoring participants in the study.

Table 4.12: Score profile lowest scorer

Scale	Composite score	Classification
Cognitive	55	Extremely low
Language	77	Borderline
Motor	58	Extremely low

This participant had the lowest scores overall as presented in Table 4.12, and was diagnosed with Mosaic Down syndrome. A participant with similar scores had no genetic condition, but suffered many complications during NICU admission. The scores of this participant are shown in Table 4.13 below.

Table 4.13: Score profile low scorer

Scale	Composite score	Classification
Cognitive	55	Extremely low
Language	77	Borderline
Motor	61	Extremely low

4.8.2 Highest scoring participants

Presented below are the composite scores of three participants who had high scores on the Bayley-III scales in this study. These participants only had between two and four comorbidities during NICU admission, and the maximum duration of NICU admission was four days. Comorbidities included sepsis, HMD, MAS, PDA and pneumonia.

Table 4.14: High score profile #1

Scale	Composite score	Classification
Cognitive	105	Average
Language	112	High Average
Motor	145	Very superior

Table 4.15: High score profile #2

Scale	Composite score	Classification
Cognitive	110	High Average
Language	121	Superior
Motor	121	Superior

Table 4.16: High score profile #3

Scale	Composite score	Classification
Cognitive	120	Superior
Language	115	High Average
Motor	115	High average

The mean corrected age of the above three participants was four months and nine days at the time of the neurodevelopmental assessment.

In the following chapter, the findings of this study will be discussed.

Chapter 5: **Discussion**

The results presented in chapter 4 will be discussed in this chapter.

5.1 Results of Bayley-III neurodevelopmental assessments

5.1.1 Significance of the Bayley-III scores of this study sample

The mean language and motor composite scores of this study population were average (96 and 94 respectively), and the mean cognitive score was low average (87). There are many different definitions for developmental delay, and unanimously the definitions suggest that an infant must perform below, or worse, than their same-age peers on a developmental test for a diagnosis of developmental delay to be given. Although the Bayley-III neurodevelopmental assessment can provide relevant developmental age information interpreted as scores, it is highly recommended to assess the full clinical picture of an infant using more than one source of information before giving the diagnosis of developmental delay (Bayley 2006). On each scale of the Bayley-III an abnormal score (abnormal development) is stated as that below 70, and a score between 70 and 85 indicates risk of developmental delay (Ballot et al. 2012).

When compared to another South African study by Ballot et al. (2012), the scores of the current study are similar yet slightly higher. The study by Ballot et al. (2012) also performed the Bayley-III neurodevelopmental assessment on a comparable population group to the current study (neonatal unit survivors at follow up) but had a study sample of 106 infants. The mean composite scores on the Bayley-III assessment were as follows; 89 on the cognitive scale (low average), 88 on the language scale (low average), and 90 on the motor scale (average). Compared to the current study, only the cognitive score is higher. However, in the study by Ballot et al. (2012), the median age at assessment was 16.48 months and participants were only low birth weight infants. A similar study has not been found internationally as the studies involving NICU survivors and using the Bayley-III have very specific

inclusion criteria. The inclusion criteria in the current study is very broad, and so comparison to more specific studies is difficult.

In the current study, five participants (12.5%) have cognitive scores lower than 70 classifying these participants as having abnormal development. On the motor scale, seven participants (17.5%) are classified with abnormal development (motor scores lower than 70). No participants have language scores lower than 70, therefore no participants in this study have abnormal development across all three subscales. In the 'at risk' category (scores between 70 and 85) on the cognitive scale there are 15 participants (37.5%), on the language scale there are six participants (15%), and on the motor scale there are ten participants (25%). Compared to the study by Ballot et al. (2012) where 15.1% of infants had abnormal development on one or more subscales, the results in the current study are similar. In that study, 3.7% of infants had abnormal development in all three areas, whereas the current study had none (Ballot et al. 2012).

With the Bayley-III, using the group classifications or levels of performance (from extremely low to very superior), can be useful when comparing the performance of an infant to that of an appropriate normative group. Performance on the Bayley-III can be analysed in terms of a participant's subscale score pattern (intraindividual perspective), or compared to an appropriate normative referenced group (interindividual perspective) (Bayley 2006).

The normative data for the updated Bayley-III were collected in the United States of America, over ten months in 2004. The sample was stratified on demographic variables including age and sex of infants, geographic location and education level of the parent. The normative group included infants with specific diagnoses and genetic conditions, these being; Down syndrome, CP, preterm birth, birth asphyxia, exposure to alcohol in utero and language

impairment, among others. This specific group made up ten percent of the total included in the normative group to ensure that it was representative of a population (Piñon 2010). The Bayley-III has been validated in many countries and across many socio-economic groups including South Africa (Richter et al. 1992).

5.1.2 Lowest overall scoring participants

The lowest scoring participant was diagnosed with Mosaic Down syndrome. In roughly two percent of Down syndrome cases, mosaicism on the trisomic cell line is seen, which means that the anomaly is found on only some cells and others are unaffected (Dreux et al. 2008). This participant had poor visual awareness. The comorbidities consisted of preterm birth (31 weeks), LBW, sepsis, NNJ, NEC, IVH and anaemia. The participant received rehabilitation services during hospital admission (post-NICU discharge). This participant's score profile is described in table 4.12 in chapter four.

The participant who scored the lowest overall without a genetic condition, had many comorbidities and stayed in NICU for over a month. This participant was born preterm at 32 weeks gestational age with a birth weight of 2645 grams. He was oxygen dependent and required supplemental 'home oxygen' at the time of assessment (total of 150 days). The participant's comorbidities consisted of CLD, PVL, sepsis, seizures, anaemia, cardiac surgery for a VSD, pulmonary atresia, and large, right-sided cerebral infarcts (posterior and middle cerebral artery regions). Importantly, this participant also had meningitis during admission and was later diagnosed with cerebral palsy, microcephaly and failure to thrive. There was one subsequent admission to hospital for poor feeding and bronchopneumonia. Table 4.13 in chapter four shows the scores of this participant.

5.1.3 Highest overall scoring participants

Three participants had equally high scores. The most comorbidities that occurred in any of these participants was four, with the mean number of comorbidities being two. They included sepsis, HMD, MAS, PDA and pneumonia. The maximum number of days that these participants spent in NICU was four. This is in direct contrast to the lowest scorers who had many complications and longer admissions to NICU. The composite scores in this high-achieving category ranged from high-average to very superior. These participants were all above 32 weeks gestational age, and their birth weights were above 1700 grams.

5.2 Statistically significant associations

In the statistical analysis, using the Chi-squared test, various associations were found between risk of neurodevelopmental delay and patient characteristics or experienced complications. The small sample size must be taken into account when interpreting these data.

5.2.1 Sepsis and cognitive delay

Sepsis during NICU admission was significantly associated with risk of abnormal cognitive development (P=0.018). Sepsis was found to be the most frequent complication during NICU admission, occurring in 67.5% of participants. Sepsis may harm the developing brain and lead to neurological complications such as PVL and ultimately poor neurodevelopmental outcomes (Schlapbach et al. 2011). In a very large cohort study conducted by Mitha et al. (2013), infants who had various confirmed pathogens in the neonatal period were assessed at five years old. The results showed that the frequency of CP was nine percent and that of intellectual impairment was 12%. They found this result to be consistent with the neurotoxic effects of infectious or inflammatory mediators on cerebral white matter (Mitha et al. 2013).

Preterm infants have a much higher risk (11 times greater) of infection compared to term infants, as their defence mechanism against infection is underdeveloped. Within the first three days of life, infection is classified as early-onset sepsis, and from four days of life it is classified as late-onset sepsis. Silva et al. (2015) conducted a prospective cohort study in an NICU in Brazil, including 30 infants (mean gestational age of 28 weeks) and documented a number of characteristics. Forty-seven percent of infants in the study were diagnosed with late-onset sepsis. Risk factors for neonatal sepsis in this study were listed as immunological immaturity of the study population, mechanical ventilation, CPAP, and other invasive procedures such as central venous catheters (Silva et al. 2015). In comparison to the current study, the incidence of sepsis in the Brazilian study was lower. Ballot et al. (2012) also present a very low percentage of sepsis during hospital admission (13.3%) in their study of infants discharged from a neonatal unit, compared to the current study. However, the study included not only infants admitted to the NICU but also infants from the neonatal high care section and ward.

Infants in an NICU who have greater birth weight and gestational age are still at risk of late-onset sepsis (predominantly nosocomial sepsis) although to a lesser extent than LBW and preterm infants (Silva et al. 2015). In addition to this, there is a high turnover of infants in the NICU (596 admissions in 2014). There is also an extremely high number of births in the obstetric theatres and labour ward (20,137 live births in 2014), which are both operational for 24 hours a day, 365 days a year and are difficult to close down for disinfecting frequently (Nakwa 2015).

5.2.2 NVD and motor delay

Birth via NVD was found to be significantly associated with risk of abnormal motor development (P=0.004). At CHBAH the majority of pregnant women who attend the antenatal clinic are categorised as high risk, needing a tertiary level of care. Torabi et al. (2012) describe a high risk pregnancy as one in which the mother, foetus, or infant possibly encounter death, disability or

disease. The most significant factors for these risks are preeclampsia, placental abruption, intrauterine growth restriction, maternal malnutrition and disease, pregnancy at the extremes of child-bearing age, and more than five previous pregnancies. At CHBAH, the deliveries that are deemed to be very high risk or doctors predict possible complications, are booked for Caesarean section delivery. This is to minimise the complications that may arise for the infant and the mother. In essence, these infants are monitored perinatally owing to the known risk factors of the pregnancy or delivery. By delivering in a more controlled environment the risk of possible expected complications is lessened. In contrast to this, the majority of mothers delivering via normal vaginal delivery either have minimal or no risk factors and doctors deem an NVD to be safe, or deliver in an emergency before the scheduled date of delivery due to unforeseen complications. There is also a percentage of mothers who are not attending the antenatal clinic at CHBAH and have not been assessed for possible risk factors. These mothers usually present at their local clinic when they are in labour, complications are realised and they are referred to CHBAH for delivery and often give birth in the ambulance without a doctor or midwife. Others in this situation will choose to go straight to CHBAH if they are in the vicinity, and the delivery is not planned or prepared, leaving medical staff to deal with unpredicted complications. These explanations above could be the reason for NVD in this study population being a risk for abnormal motor development (P=0.004) as complications are unforeseen. In this study the percentage of preterm deliveries via NVD was 63.1%, confirming that these deliveries were unexpected and possibly proceeded without medical staff being fully prepared.

5.2.3 Anaemia and motor delay

Although blood transfusion is known to be associated with infectious and noninfectious risks, little is known about the long-term consequences of neonatal anaemia and its treatment (Widness 2008). Detrimental symptoms have been linked with anaemia in infants, such as tachycardia, poor weight gain, apnoea, and lactic acidosis (Valieva et al. 2009). Severe neonatal anaemia can impair cerebral oxygen supply, yet data on long-term outcomes

following severe neonatal anaemia are scarce (Zonnenberg et al. 2016). In a study by Zonnenberg et al. (2016) MRI was performed on infants with severe anaemia. Results showed that some form of white matter injury was found in 64% of patients, as well as predominant patterns of injury in the basal ganglia and thalami. The infants were followed up between 14 and 35 months of age and neurodevelopment was assessed using the Griffiths Scale of Mental Development or the Bayley Scales of Infant Development. Outcomes of the tests were within the normal range for the majority of infants in the study (Zonnenberg et al. 2016).

In the current study, anaemia during NICU admission was significantly associated with abnormal motor development (P=0.038). The abovementioned effects that neonatal anaemia has on infants may serve as an explanation to the results found in this study.

5.3 Participant demographics and histories

5.3.1 Demographics of the population

At CHBAH, the minimum weight for admission into NICU is 1000 grams. If the infant's problems are purely respiratory, the NICU will accept an infant of 900 grams. There were two participants in this study with birth weights of less than 900 grams, who may have been admitted to NICU at a later stage (i.e. greater than 1000 grams) when complications arose.

The assessments were carried out over an eight month period, and corrected ages at the time of assessment varied greatly with a standard deviation of 38 days from the mean corrected age of 147 days. As the NNFUC is held weekly, caregivers often do not follow their given dates precisely and all the infants attending the clinic are of vastly different ages. Having an equal number of boys and girls was unintentional but is a good representation of infants attending the clinic. The maternal age was also over a wide range with three mothers of 17 years and two mothers of 39 years old, the mean

maternal age being 28 years. This is comparative to the median maternal age found in the study also conducted in Gauteng by Ballot et al. (2012), which was 26 years (Ballot et al. 2012).

5.3.2 HIV

Almost one third (32.5%) of the participants in this study were exposed to HIV, which is comparable to 32.4% of infants who were exposed to HIV in a similar study conducted by Ballot et al. (Ballot et al. 2012). This is possibly due to similar characteristics of the mothers in each study attending similar hospitals, CHBAH and Charlotte Maxeke Johannesburg Academic Hospital (CMJAH). These two hospitals serve patients of largely the same socio-economic status, both in large cities in Gauteng.

Only one participant in this study's population had HIV infection. This participant's mother only initiated ARV's after five months of pregnancy. The HIV positive participant (three months and 23 days old at the time of assessment) was on combination ARV's consisting of 3TC (lamivudine), ABC (abacavir) and Kaletra (lopinovir/ritonavir). The gestational age and birth weight were in a normal range, 39 weeks and 2990 grams respectively. This participant did have a number of complications during and after NICU admission, however, the length of stay in NICU was only six days. The complications included; congenital pneumonia, hyperthyroidism, renal dysfunction, bilateral pneumothoraces, anaemia, hypotension, hypokalaemia and dermatological complications. The Bayley-III scores that this participant achieved were average (cognitive and language scales) and low average (motor scale).

5.3.3 Growth

The majority of participants in the study had weight-for-age and length-for-age values within normal limits (WHO 2008). Z-scores of below minus three for weight were documented in 12.5% of participants and Z-scores of below

minus three for length were documented in 22.5% of participants in this study. A systematic review was conducted in South Africa reviewing the prevalence of stunting (length-for-age) of children less than six years of age (Said-Mohamed et al. 2015). Authors concluded that stunting still persists in the country at a significant level, despite economic transition over the past 40 years (Said-Mohamed et al. 2015).

5.3.4 Non-medical interventions

The CHBAH NICU does not practise Kangaroo Mother Care (KMC), however in the step-down wards it is part of a patient's management where appropriate. The aim of KMC in the CHBAH neonatal wards is largely promotion of weight gain and infants must be deemed medically stable. This may account for the low percentage (5%) of participants in this study who partook in KMC as most of the participant's medical recoveries were long and it is likely that their weight was sufficient by the time they were stable.

Infants in the neonatal unit are treated by speech therapy and physiotherapy on a referral basis, and there are always more infants in need of feeding assessments post-NICU discharge than infants in need of a musculoskeletal or neurological assessment. This is because during the critical post-NICU period, management is still aimed at "life-saving" rather than rehabilitation. Once infants are physiologically stable they can be referred to physiotherapy if it is needed, yet due to the high number of infants, medical staff tend to refer to physiotherapy if there is an obvious abnormality or neurological fallout and not necessarily for early developmental screening. Hence, at the NNFUC visits it is vitally important to screen these infants for developmental delay.

5.3.5 Longest NICU admission

The participant with the longest admission in NICU spent 135 days there (four months and 15 days). The participant was still oxygen dependent and was on 'home-oxygen' at the time of assessment. This participant was born preterm

at 27 weeks gestational age with a very low birth weight (1030 grams). There were a total of eight comorbidities diagnosed which included CLD, PDA, PVL, surgical NEC, sepsis, IVH, hyperglycaemia, and HMD. This participant had average cognitive and language scores, and a borderline motor score due to poor endurance during motor activities. The effects of CLD and supplemental oxygen dependency have been documented in other studies, and shown to have detrimental effects on neurodevelopment (Bhakta & Stark 2006; Khan-D'Angelo et al. 2012). Of note particularly is a study by Jones et al. (1995) in which a large cohort of oxygen-dependent neonates were assessed at three years of age. The results of a neurodevelopmental test showed that 35% of the population were severely disabled and 19% were diagnosed with cerebral palsy. The mean gestational age and birth weight were also low, 27 weeks and 1000 grams respectively (Jones et al. 1995)

5.4 Other frequent comorbidities and complications

5.4.1 Blood transfusions

There was a high number of blood transfusions needed in this population (55%). However only 54.5% of the transfusions were for anaemia, with no reasons given for the remaining 45.5%. Only two participants (five percent of the total) were diagnosed with thrombocytopaenia. This is an uncharacteristically low number for a population of neonates and perhaps in some cases, may not have formed part of the formal list of comorbidities due to the frequency of low platelet counts with each case. Many participants had more than one blood transfusion during their NICU admission.

Valieva et al. (2009) report on the effects of blood transfusions in neonates, in their retrospective study of 60 extremely low birth weight (ELBW) infants. The incidence of blood transfusions in the study population was 78%, considerably higher than the current study. The results showed an association between blood transfusions and BPD, NEC and diuretic use ($P<.05$) (Valieva et al. 2009). In contrast, the current study had a higher percentage of blood transfusions than the South African study by Ballot et al. (2012) which had a

sample of 106 infants, where the percentage of blood transfusions was 30.2%.

5.4.2 Neonatal jaundice

NNJ, or hyperbilirubinaemia, was diagnosed in 37.5% of participants, and is a well-documented complication in neonates (Khan-D'Angelo et al. 2012). The mean birth weight in this group was 1649 grams and mean gestational age was 32 weeks. All infants were treated with phototherapy and recovered timeously, with no cases advancing to kernicterus thus not directly causing abnormal neurodevelopment in this population. Exchange transfusion was not reported as a treatment for any of the participants.

In the Netherlands, a stratified cohort of 832 neonates (gestational ages between 32 and 35 weeks) was analysed (Kerstjens et al. 2012). Associations between neonatal morbidities and developmental delay were assessed. In the study, the incidence of neonatal hyperbilirubinaemia was 46.4%, slightly higher than the current study. Hyperbilirubinaemia was not associated with developmental delay in the study (Kerstjens et al. 2012).

5.4.3 Hyaline membrane disease

In this study, 37.5% of infants were diagnosed with HMD. Included in this group, was the participant with the longest oxygen dependency. The mean length of supplemental oxygen in participants with HMD was 41 days, with a standard deviation of 61 days. Interestingly, also included in this group were the two participants who were diagnosed with ROP. ROP is known to be associated with the need for increased fractions of inspired oxygen, and all neonates requiring supplemental oxygen at CHBAH are screened for ROP (Khan-D'Angelo et al. 2012). Similarly to the NNJ group, the group with HMD had a mean gestational age of 32 weeks and mean birth weight of 1642 grams. Respiratory distress syndrome (RDS) and HMD are two names for the same condition, and are used interchangeably in the CHBAH NICU. In the

results they are shown as two different variables as it was recorded in the participants' hospital files.

5.4.4 Hypoxic ischaemic encephalopathy and neonatal encephalopathy

In this study population, three participants were diagnosed with HIE I (seven point five percent). All three were born at full term, 40 weeks gestational age or more. Only one participant with HIE I had low scores on the Bayley-III neurodevelopmental assessment. HIE I is the mildest form of HIE and usually results in very few complications (Robertson & Perlman 2006).

One participant was diagnosed with neonatal encephalopathy which was complicated by seizures, however, apgar scores were nine and ten for one and five minutes respectively. This participant's gestational age was 39 weeks, and only motor scores on the Bayley-III neurodevelopmental assessment were below average. The cause of neonatal encephalopathy is often unknown (The American College of Obstetricians and Gynecologists 2014).

5.4.5 Musculoskeletal complications

One participant had a femur fracture at the time of assessment (six months and 27 days corrected age). A family member had fallen onto the infant while carrying them. There was no associated head injury, and the fracture was being managed conservatively in a plaster of paris cast. This participant had low scores on the Bayley-III neurodevelopmental assessment, however also had a plethora of complications during the NICU admission.

5.5 Implications of the study

From the results obtained in this study it is evident that there are many complications which may be experienced during admission to an NICU. Coupled with the effects of the harsh environment, these complications may

put an infant at risk for developmental delay or abnormal development. The mean neurodevelopmental assessment scores in this population were not favourable, showing low average or average performance. As shown, it is imperative for this high-risk population of infants to attend a follow up service where their neurodevelopment can be assessed by a therapist. In cases where intervention is necessary, it can be initiated during these follow up visits and further planning of therapy services can be done together with the caregiver.

Of importance, is the duration of stay in NICU and even more so, the duration of oxygen dependency. If not screened timeously, allowing early intervention to commence, these infants are at high risk for delayed neurodevelopment in one or more areas. The number of complications encountered by an infant is also a 'red-flag' for early detection and intervention, with higher numbers of complications putting infants at a greater risk for adverse neurodevelopment.

It is clear from the results of this study that infants who are diagnosed with a genetic condition or congenital abnormality should be assessed as soon as possible for neurodevelopmental delay. A clear therapy plan should be discussed with the family and intervention should start immediately.

All infants with known neurological conditions or neurological fallout of different causes should be assessed by a therapist for neurodevelopmental delay, as shown in this study. It is also recommended that infants who have undergone major surgery, attend a follow up visit where they too can be assessed for neurodevelopmental delay.

This study may guide therapists working in an NICU or neonatal unit and at follow up clinics, as to how to identify infants who need timeous neurodevelopmental screening or therapeutic intervention. It may also guide

doctors when deciding on which infants are most in need of neurodevelopmental assessments, particularly during a busy clinic with many infants presenting for follow up.

5.6 Limitations of the study

This study looked at an age range between three and seven months corrected age, which is young. This fact may have been a limitation as infants have perhaps not reached their true potential developmentally. Also associated with this limitation is that not all conditions, for example CP, may be diagnosed before seven months and the low rate of CP in this study population (5%) may be inaccurate. Infants were not followed up subsequently at different ages, limiting the Bayley-III results to one assessment only.

The lowest scoring participant had Mosaic Down Syndrome, causing the neurodevelopmental assessment results to be extremely low. Including this patient in the study could be seen as a limitation as he was at a true disadvantage developmentally.

Although the Bayley-III neurodevelopmental assessment is normative referenced and valid and reliable in the South African context, another limitation of this study is that there was no control group of infants who were not admitted to the NICU.

5.7 Recommendations for further research

This study demonstrates that neurodevelopmental assessment and screening of high-risk infants is important, in order to start appropriate early intervention when it is needed. However, this study only included infants discharged from an NICU. It is recommended that a larger study be done, including infants not only from NICU but also from high care and the general neonatal ward. It is

also recommended that neurodevelopmental assessments be carried out at different ages for a long-term period, which will give a more accurate picture of an infant's neurodevelopment as well as identify significant risk-factors for adverse neurodevelopment. Intervention strategies then need to be implemented timeously where needed, to facilitate normal development and optimal functioning of an infant.

The statistical analysis of this study suggests that in a larger study, inclusion should focus on infants with sepsis, those born via NVD and those who had anaemia. Other complications to pay close attention to are IVH, low birth weight, PDA and RDS. A larger study would also be recommended to assess the effects of NNJ, NEC and twin or triplet pregnancy as these factors showed trends in the current study for being almost significant risk factors for abnormal neurodevelopment.

Chapter 6: **Conclusion**

Literature describes the significant effect that admission to an NICU can have on an infant's neurodevelopment (Leppert & Allen 2012; Pineda et al. 2014). During the most critical stage of an infant's neurodevelopment, they may be exposed to the harsh environment of an NICU and are extremely vulnerable to the adverse effects of neonatal complications and certain life-saving procedures (Pineda et al. 2013; Massaro et al. 2006). These fragile infants are at risk of adverse neurodevelopment, and it is highly recommended that they are assessed with an appropriate neurodevelopmental assessment by a trained professional during their early childhood until school-going age (Leppert & Allen 2012; Hilderman & Harris 2014; Greene et al. 2013). In the instance where neurodevelopment is found to be abnormal, early developmental intervention can commence (Spittle et al. 2012; Vanderveen et al. 2009; Litt & Perrin 2014).

The aim of this study was to conduct neurodevelopmental assessments on infants who graduated from the NICU at CHBAH in Gauteng. Measuring physical growth and documenting birth and clinical data were objectives of this study.

The 40 participants in the study were assessed at a corrected age between three and seven months by a physiotherapist, using the Bayley Scales of Infant and Toddler Development. The neurodevelopmental assessments were conducted at the NNFUC which runs once a week at the hospital. Results were analysed together with the birth history and clinical data of each participant, as well as growth measurements. Early intervention was implemented for participants who showed risk of developmental delay, however all caregivers were educated on how to facilitate normal development, regardless of assessment outcome. Participants were not followed up again.

When analysing the results of this study it is clear that infants who had fewer complications during NICU admission had higher neurodevelopmental scores on the

Bayley-III. Infants who had many (or more than four) complications in NICU were more likely to have lower scores on the Bayley-III assessment. In the same token, infants in this population who had a shorter admission to NICU scored higher than those who had lengthy admissions in NICU. This would suggest that particular attention should be paid to infants with long durations of stay and several comorbidities or complications, after discharge, and it is highly recommended that these infants undergo formal neurodevelopmental assessment.

While it is not possible from the results of this study to determine which factor or complication *independently* poses a risk for abnormal neurodevelopment, they can be highlighted from the data of the lowest scoring participants as well as the statistically significant data. The results of the statistical analysis suggest that particular attention should be paid to infants diagnosed with sepsis, anaemia and those born via NVD when planning follow-up assessment and intervention. As evidenced by the descriptive analysis, infants diagnosed with a genetic condition should be referred to a therapy service when they are deemed medically stable, so as to begin early intervention as soon as possible. Infants with neurological sequelae and those with conditions requiring surgery are also high-priorities for neurodevelopmental screening and early intervention.

However, the mean Bayley-III scores of the population presented in this study (ranging from low average to average) would suggest that all infants who are discharged from an NICU are at risk for a degree of neurodevelopmental delay. Ideally all these infants should be assessed using a formal neurodevelopmental test.

As stated in the beginning of the study, time and resources are limited in the NNFUC setting at CHBAH and at many other state hospitals in South Africa. This research may serve as a guide to therapists, doctors and other health care workers when prioritising infants in need of neurodevelopmental assessment and therapeutic services.

Chapter 7: **References**

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Appendix 1

Information sheet

The neurodevelopmental outcomes of Neonatal Intensive Care Unit survivors attending the Neonatal Follow Up Clinic at a central academic hospital in Gauteng.

Dear Parent

My name is Samantha Rosie, I am a physiotherapist at Chris Hani Baragwanath Academic Hospital. I am currently conducting a study as part of a Master's degree in Physiotherapy being done through the University of the Witwatersrand. The research will serve to help us understand how babies develop if they have spent time in ICU. This information will aid in identifying which babies will need therapy in order to promote normal development.

I am asking permission to use your baby's hospital file to collect information regarding their admission. Weight and height measurements will be taken and then a detailed assessment will be performed to assess their development. This will take approximately 45 minutes. The assessment has 3 stages; motor, language and cognition. You will be able to ask questions at any time.

All the personal information will be kept confidential and no information that could identify your child will be used in the research report. Participation in the study is voluntary. You may withdraw from the study at any stage and there will be no adverse consequences to any person if you refuse to participate or withdraw your participation. There are no risks involved in the study, nor direct benefits.

Thank you for your time.

If there are any questions or if you require more information, please contact the researcher.

Samantha Rosie

Physiotherapy department - Chris Hani Baragwanath Academic Hospital

Contact: 0828272260

0119338309 / 8818

Human Research Ethics Committee (Medical) (HREC) contact: 011-717-2700

Appendix 2

Consent Form

I _____, hereby give consent for my child _____ to be assessed for the study entitled: The neurodevelopmental outcomes of Neonatal Intensive Care Unit survivors attending the Neonatal Follow Up Clinic at a central academic hospital in Gauteng. I give permission to the researcher to access my child's hospital records.

I may change my mind at any time.

I understand that there are no risks involved in this study.

Signed	Witness
_____	_____
Date:	Date:
Place:	Place:

Appendix 3

HISTORY

STUDY CODE:

DOB:	BW: CW:
Gestational age:	Length:
Chronological age:	Head circ.:
Corrected age:	Maternal age:
Gender:	Maternal drugs:
Apgar 1 min.:	Apgar 5 min.:
Mode of delivery:	ICU adm. date:
ICU LOS:	Step down ward:
Time to d/c:	Mode of vent./O_2:
Duration of vent./O_2:	Feeding method:
Resus. Details:	Cranial U/S report:

Circle:

RVD exp.:	Yes / No	NNJ:	Yes / No
PCR pos.:	Yes / No	NEC:	Yes / No
KMC:	Yes / No	Surgery:	Yes / No
PDA:	Yes / No	RDS:	Yes / No
CLD:	Yes / No	MAS:	Yes / No
HMD:	Yes / No	NE:	Yes / No
PVL:	Yes / No	IVH:	Yes / No
CVA:	Yes / No	HIE:	Yes / No
PA:	Yes / No	T/F:	Yes / No
Sepsis:	Yes / No	Seizures:	Yes / No
Multi preg.:	Yes / No	Allied rx:	Yes / No

Other complication: _____

_____

Other abnormality: _____

_____

Appendix 4:

Protocol

The neurodevelopmental outcomes of Neonatal Intensive Care Unit survivors attending the Neonatal Follow Up Clinic at a central academic hospital in Gauteng.

Samantha Rosie BSc Physiotherapy (Wits)

0704379G

Supervisors: Prof. J Potterton

S Pilusa

Contact: samc.rosie@gmail.com

0828272260

Introduction:

Over the past four decades, neonatology has made astounding advances in intensive care which has improved outcomes and survival of premature infants and infants with serious medical and surgical conditions (Browne 2011; Khan-D'Angelo et al. 2012). These infants are termed *high risk.* Most commonly, *high risk* refers to the likelihood of neurodevelopmental disability, which is a group of interrelated, chronic, non-progressive disorders of the central nervous system caused by injury to or malformation of the developing brain (Leppert & Allen 2012).

The long term effects that the neonatal intensive care unit (NICU) environment as well as varying neonatal morbidities have on NICU graduates may be detrimental (Pineda et al. 2014; Leppert & Allen 2012) . NICU graduates may present later in infancy or childhood with different degrees of developmental delay, or other long term complications. Severity and number of complications can be used to identify infants at high risk for disability (Leppert & Allen 2012). Neonates in an ICU environment are among the most fragile patients that physiotherapists will assess and treat, and detrimental effects can occur with routine medical or nursing procedures (Khan-D'Angelo et al. 2012).

Aly et al. (2010) define developmental delay as the inability of a child to acquire developmental milestones at the expected age, 'age-appropriate' functionality, even after allowing for the broad variation of normality. It may be restricted to one domain or be a global developmental delay. Early identification of infants with developmental delay or disabilities will lead to treatment and interventions, which can lessen the impact on the functioning of the child (Aly et al. 2010).

When assessing an infant's development there are many standardised assessment tools available, many of which are not validated for use in under-resourced settings in a developing country. The most widely used standardised and norm-referenced tool is the *Bayley Scales of Infant Development* (Whitehead et al. 2013). It is a set of developmental scales designed to measure developmental functioning. The most

recent version is the *Bayley Scales of Infant and Toddler Development third edition (Bayley III)* (Lennon et al. 2008). It was released in 2006, and has since been shown to be both valid and reliable (Bayley 2006; Whitehead et al. 2013). This edition can be used to assess infants with below normal birth weights and earlier gestational age, as well as significant neonatal risk factors. The *Bayley III* assesses components such as motor, language, and cognitive development (Lennon et al. 2008).

NICU graduates, who are at risk of poor neurodevelopmental outcomes, need to attend comprehensive follow up appointments (Maitre et al. 2013). Many babies who attend such clinics and do not present with obvious neurological deficits or developmental delay, are often not referred to allied services such as physiotherapy. Many of these cases that appeared in infancy to be normal, present at later ages with subtle disorders such as attention deficit and specific learning disorders (Gücüyener et al. 2006). It is therefore important that all NICU graduates attend a follow up clinic and undergo developmental screening as early as possible, where a multidisciplinary approach may be implored to facilitate normal development. Some deficits such as poor vision, hearing deficits, cerebral palsy, and other significant developmental delay appear earlier and appropriate early intervention can commence (Gücüyener et al. 2006).

In 2012, there were 22592 live births at Chris Hani Baragwanath Academic Hospital (CHBAH) (Nakwa 2012). Of these, 699 were admitted over the year to the 12 bed NICU. At this hospital there is a dedicated Neonatal Follow Up Clinic (NNFUC) that runs once a week. NICU graduates return at six weeks post discharge or earlier where necessary. Also included in this clinic are babies who were admitted at the hospital post-natally, but not admitted to NICU. In 2013, a total of 3630 babies attended the NNFUC, giving an average of 303 babies a month.

All allied disciplines provide a service in the NNFUC, including physiotherapy, occupational therapy, speech therapy, audiology and dietary. There is a high load of

patients attending the clinic and unfortunately not all babies receive developmental screening. Developing countries such as South Africa readily adopt the afore-mentioned advances in neonatal care but fail to provide the adequate follow up that is needed for high risk infants. This leads to a significant contrast in the level of care received in NICU and at follow up clinics which are often poorly resourced (Ballot et al. 2012).

Problem statement:

It is important to identify high risk infants who could benefit from developmental screening, as well as early intervention where needed. The NNFUC at CHBAH has inadequate staffing, time, clinical space, equipment, and basic amenities. Therefore a streamlined and comprehensive way of developmental screening would be beneficial in view of these limitations. Assessing the neurodevelopmental outcomes of the NICU graduates and identifying the most high risk infants, would aid this process.

Research question:

What are the neurodevelopmental outcomes of NICU graduates at CHBAH?

Aim:

To assess the neurodevelopmental outcomes of babies discharged from the CHBAH NICU when they attend the NNFUC.

Objectives:

4. To assess neurodevelopmental outcomes at 3 months corrected age or at the corresponding follow up appointment between 3 and 6 months
5. To measure physical growth since NICU discharge at follow up

6. To identify associations between neurodevelopmental outcomes and birth history and clinical data

Method:

1. Study Design

This is a cross-sectional observational study.

2. Study population

Participants will include NICU graduates attending the NNFUC at CHBAH from September 2014 to July 2015, where screening will be performed to identify eligible participants.

3. Inclusion Criteria

Babies who have graduated from the NICU at CHBAH.

4. Exclusion Criteria

Babies diagnosed with Hypoxic Ischaemic Encephalopathy (HIE) II and HIE III are excluded, as they attend a different follow up clinic. Babies who were admitted only to the Neonatal Theatre unit are excluded as they attend a different follow up clinic.

5. Study sample

Statistics have been used to calculate a study sample. In 2012 there were a total of 699 babies admitted to the NICU at CHBAH, giving a mean of 58 babies admitted monthly. Based on a population of 700 babies a year with a confidence interval of 15 and a 95 percent confidence level, a sample of 40 participants is needed for this study.

6. Ethical clearance

Ethical clearance will need to be obtained from the Committee for Research on Human Subjects of the University of the Witwatersrand. Permission will need to be

granted by CHBAH to conduct the research on the premises and on patients of this hospital. Informed written consent will need to be obtained from the caregiver of each participant. This will be translated where necessary. All information and records collected from participants will be used solely for the purpose of the study, and will be kept confidential. Privacy of participants will be respected in a closed room.

7. Measurement tools

Developmental assessment tool: *Bayley Scales of Infant and Toddler Development Third edition*

Weight: The *SECA* infant weighing scale

Length: The *DEAN* infant measuring board

Head circumference: Standard measuring tape

Clinical data: Data sheet

8. Procedure

Participants will be screened at the NNFUC once a week. If their corrected age is between 3 and 6 months, and they meet the inclusion criteria, the caregiver will be invited to participate. This is their regular follow up appointment therefore there will be no extra transport cost for caregivers.

Caregivers attending the clinic with the baby will be given an information sheet explaining the research study and assessment. If they agree to their baby participating in the study, they will be given a consent form to sign. The participant and caregiver will be invited into a closed room where privacy can be respected.

All birth history will be collected and recorded on the history form. This clinical data remains with the patient in their hospital file after discharge from hospital. Any subsequent admissions to hospital are also recorded in the hospital file. All this data is with the caregiver at follow up. Weight, length and head circumference will be

measured and recorded. A neurodevelopmental assessment will be carried out on the participant, using the *Bayley III*. The assessment tool will be explained to the caregiver beforehand. Each scale, namely motor, language and cognition, will be administered to participants. In cases where participants are born preterm, the participant's age will be corrected (adjusted) using 40 weeks gestation as the full term reference. Standard scores are derived by referring to the norms table appropriate for this adjusted age (Lennon, et al., 2008). The researcher will do all of the assessments. The researcher is trained in the use of this tool and has performed these assessments in another study. The results will be recorded on the outcomes form.

All participant information will be kept in a filing system and kept confidential.

9. Data Analysis

Descriptive statistics e.g. mean and standard deviations will be used to describe the demographic characteristics of the population. Frequencies will be used to summarise the medical histories of the participants. The scores from the *Bayley III* will be presented as means and standard deviations. A regression analysis and correlations will be used to determine whether there are any relationships between demographic and clinical data and the *Bayley* scores.

Scoring is as follows (Bayley, 2006), and will be presented in a table.

Qualitative descriptions of composite scores from each domain

130 and above	Very Superior
120-129	Superior
110-119	High Average
90-109	Average
80-89	Low average
70-79	Boarderline
69 and below	Extremely low

10. Budget

Photocopying of forms (as attached): (3 x 40) x 25c = R30

Photocopying of assessment forms: (50 x 40) x 25c = R500

Total = R530

11. Timeline

2014

	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sept	Oct	Nov	Dec
Protocol submission												
Protocol assessment												
Present to dept.												
Ethics submission												
Data collection												

2015

	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sept	Oct	Nov	Dec/ Jan 2016
Data collection												
Data analysis												
Write up/submission												

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R14/49 Ms Samantha Rosie

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M140865

NAME: (Principal Investigator) Ms Samantha Rosie

DEPARTMENT: Physiotherapy
Chris Hani Baragwanath Academic Hospital

PROJECT TITLE: The Neurodevelopmental Outcomes of Neonatal Intensive Care Unit Survivors attending the Neonatal Follow Up Clinic at a Central Academic Hospital in Gauteng

DATE CONSIDERED: 29/08/2014

DECISION: Approved unconditionally

CONDITIONS:

SUPERVISOR: Joanne Potterton

APPROVED BY: Professor P Cleaton-Jones Chairperson, HREC (Medical)

DATE OF APPROVAL: 09/01/2015

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by Samantha Rosie

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The neurodevelopmental outcomes of Neonatal Intensive Care Unit survivors attending the Neonatal Follow Up Clinic at a central academic hospital in Gauteng.

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of

Master of Science in Physiotherapy

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Abstract

Background: Neonatology has made astounding advances in intensive care which has improved outcomes and survival of infants with serious medical and surgical conditions (Browne 2011; Khan-D'Angelo et al. 2012; Purdy & Melwak 2012). The long term effects that the NICU environment, as well as varying neonatal morbidities, have on NICU graduates may be detrimental to neurodevelopment (Pineda et al. 2014; Leppert & Allen 2012). Developing countries such as South Africa readily adopt the afore-mentioned advances in neonatal care but fail to provide the adequate follow up that is needed for high risk infants (Ballot et al. 2012).

Aim: To assess the neurodevelopmental outcomes of babies discharged from the Chris Hani Baragwanath Academic Hospital NICU when they attend the neonatal follow up clinic.

Methods: 40 participants were assessed according to corrected age, using the *Bayley Scales of Infant and Toddler Development Third edition*.

Results:

Data from 20 male and 20 female participants were analysed. The mean corrected age at time of assessment was 147 days (±38). The mean cognitive score was 87 (Low average), mean language score was 96 (Average) and mean motor score was 93 (Average). It was found that participants with sepsis during NICU admission were at risk of abnormal cognitive development (P=0.018) at a 5% level of significance. On the language scale, no characteristics were significant at P=0.05. However PDA (P=0.076) and RDS (P=0.057) were found to be risk factors for abnormal language development at a 10% level of significance. Participants born via NVD (P=0.004) and those who experienced anaemia (P=0.038) during NICU admission were found to be at risk of abnormal motor development, at a 5% level of significance. Twenty

one percent of participants had confirmed neurological fallout. Two participants were diagnosed with CP

Conclusion: From the results of this study it is clear that infants who had fewer complications during NICU admission had higher neurodevelopmental scores on the Bayley-III. Infants who had many (or more than four) complications as well as a long duration of stay in NICU were more likely to have lower scores on the Bayley-III assessment. However, the mean Bayley-III scores of the population presented in this study (ranging from low average to average) would suggest that all infants who are discharged from an NICU are at risk for a degree of neurodevelopmental delay.

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Declaration

I declare that this research is my own work. It is being submitted in partial fulfilment of the requirements for the degree of Master of Science in Physiotherapy. It has not been submitted before for any other degree or examination at this or any other university.

Samantha Rosie

18th day of March 2016

List of abbreviations

BW:	Birth weight
CW:	Current weight
RVD exp.:	Retroviral disease exposed
NNJ:	Neonatal jaundice
NEC:	Necrotising enterocolitis
KMC:	Kangaroo Mother Child Care
PDA:	Patent ductus arteriosis
RDS:	Respiratory distress syndrome
CLD:	Chronic lung disease
MAS:	Meconium aspiration syndrome
HMD:	Hyaline membrane disease
NE:	Neonatal encephalopathy
PVL:	Periventricular leukomalacia
IVH:	Intraventricular haemorrhage
CVA:	Neonatal stroke
HIE:	Hypoxic ischaemic encephalopathy
PA:	Perinatal asphyxia
T/F:	Blood transfusion
LOS:	Length of stay
Multi. Preg.:	Multiple pregnancy
NVD:	Normal vaginal delivery
IPPV:	Intermittent positive pressure ventilation
NPO_2:	Nasal prongs oxygen
NCPAP:	Nasal continuous positive airway pressure
HFOV:	High frequency oscillatory ventilation
ARV's:	Antiretrovirals

Presentations

1. Gauteng Association for Infant Mental Health Conference

   Title of presentation:

   The neurodevelopmental outcomes of Neonatal Intensive Care Unit survivors attending the Neonatal Follow Up Clinic at a central academic hospital in Gauteng.

   By Samantha Rosie and Joanne Potterton

   Presented by Samantha Rosie

   31 October 2015

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Chapter 1: **Introduction**

1.1 Background

Over the past four decades, neonatology has made astounding advances in intensive care which has improved outcomes and survival of premature infants and infants with serious medical and surgical conditions (Browne 2011; Khan-D'Angelo et al. 2012; Purdy & Melwak 2012). These infants are termed *high risk*. Most commonly, *high risk* refers to "the likelihood of neurodevelopmental disability, which is a group of interrelated, chronic, non-progressive disorders of the central nervous system caused by injury to or malformation of the developing brain" (Leppert & Allen 2012, pp. 920).

The long term effects that the neonatal intensive care unit (NICU) environment as well as varying neonatal morbidities have on NICU graduates may be detrimental (Pineda et al. 2014; Leppert & Allen 2012). NICU graduates may present later in infancy or childhood with different degrees of developmental delay, or other long term complications. Severity and number of complications can be used to identify infants at high risk for disability (Leppert & Allen 2012). Neonates in an ICU environment are among the most fragile patients that physiotherapists will assess and treat, and detrimental effects can occur with routine medical, physiotherapeutic or nursing procedures (Khan-D'Angelo et al. 2012).

Aly et al. (2010) define developmental delay as the inability of a child to acquire developmental milestones at the expected age, 'age-appropriate' functionality, even after allowing for the broad variation of normality. It may be restricted to one domain or be a global developmental delay. Early identification of infants with developmental delay or disabilities will lead to treatment and interventions, which can lessen the impact on the functioning of the child (Aly et al. 2010; Hoekelman & Simeonsson 1992).

NICU graduates, who are at risk of poor neurodevelopmental outcomes, should attend comprehensive follow up appointments (Maitre et al. 2013; Hilderman & Harris 2014). Many babies who attend such clinics and do not present with obvious neurological deficits or developmental delay, are often not referred to allied services such as physiotherapy. Many of these cases that appeared in infancy to be normal, present at later ages with subtle disorders such as attention deficit and specific learning disorders. It is therefore important that all NICU graduates attend a follow up clinic and undergo developmental screening as early as possible, where a multidisciplinary approach may be employed to facilitate normal development (Greene et al. 2013). Some deficits such as poor vision, hearing deficits, cerebral palsy, and other significant developmental delay appear earlier and appropriate early intervention can commence (Gücüyener et al. 2006).

In 2014, there were 20 137 live births at Chris Hani Baragwanath Academic Hospital (CHBAH). Of these, 596 were admitted over the year to the 12 bed NICU (Nakwa 2015). At this hospital there is a dedicated Neonatal Follow Up Clinic (NNFUC) that runs once a week. NICU graduates return at six weeks post discharge or earlier where necessary. Also included in this clinic are babies who were admitted at the hospital post-natally, but not admitted to NICU. In 2014, a total of 4535 babies attended the NNFUC, giving an average of 412 babies a month as the clinic is closed at the end of December and the beginning of January.

All allied disciplines provide a service in the NNFUC, including physiotherapy, occupational therapy, speech therapy, audiology and dietetics. There is a high load of patients attending the clinic and unfortunately not all babies receive developmental screening. Developing countries such as South Africa readily adopt the afore-mentioned advances in neonatal care but fail to provide the adequate follow up that is needed for high risk infants. This leads to a significant contrast in the level of care received in NICU and at follow up clinics which are often poorly resourced (Ballot et al. 2012).

1.2 Research question

What are the neurodevelopmental outcomes of NICU graduates at CHBAH?

1.3 Aim

To assess the neurodevelopmental outcomes of infants discharged from the CHBAH NICU when they attend the NNFUC.

1.4 Objectives

1.4.1 To assess neurodevelopmental outcomes once, between three and seven months corrected age

1.4.2 To measure physical growth since NICU discharge at follow up

1.4.3 To identify associations between neurodevelopmental outcomes and birth history and clinical data

1.5 Significance of the study

It is important to identify high risk infants who could benefit from developmental screening, as well as early intervention where needed. The NNFUC at CHBAH has inadequate staffing, time, clinical space, equipment, and basic amenities. Therefore a streamlined and comprehensive way of developmental screening would be beneficial in view of these limitations. Assessing the neurodevelopmental outcomes of NICU graduates and identifying the most high risk infants, would facilitate the screening of infants in a large and busy clinic.

Chapter 2: **Literature review**

2.1 Neurodevelopment

Foetal and infant brain development is unmatched in complexity and rate, in the rest of life (Bardo 2009; White 2011). From 17 to 20 days gestation, the neural plate and neural tube form. Definition of the gyri and sulci is only complete at 35 weeks gestation (Bardo 2009). Between these two events the other brain structures are forming and neuronal differentiation and migration occurs throughout, as well as synaptic and neurochemical development (Massaro et al. 2006). This neurodevelopment in utero is extremely complex and is dependent on many factors including oxygen and nutrient delivery from maternal circulation. At term, or 40 weeks of gestation, myelination begins (Massaro et al. 2006). It is apparent from this knowledge of foetal brain development, that any interruption or adverse event during this intricate process could cause abnormalities or disruption in neurodevelopment. Extreme preterm birth, exposure to toxins, or an inadequate supply of micronutrients or oxygen are examples of factors that may harm neurodevelopment (Massaro et al. 2006). In an infant's first year of life, its brain volume more than doubles and this time in brain development is as critical as that in utero. Pineda et al. 2013 state that neurodevelopment can be influenced by cerebral injury and altered brain development during this vulnerable time.

2.2.1 The Neonatal Intensive Care Unit

Historically, the neonatal intensive care unit (NICU) was primarily designed for "life-saving". It was a harsh environment, survival of preterm infants was a novelty and so the effects of the environment were overlooked (White 2011). Over the past few decades there have been significant advances in medical treatments and technologies in the NICU leading to increased survival rates of preterm infants and infants with serious medical and surgical complications (Browne 2011; Khan-D'Angelo et al. 2012; Purdy & Melwak 2012).

Unfortunately, along with the greater rate of survival of these 'high risk' infants, comes the adverse effects of their immediate environment and threatening medical comorbidities. It is widely known that preterm and sick infants, in particular those who required neonatal intensive care, have an increased risk of neurodevelopmental disabilities (Leppert & Allen 2012). Complications increase as birth weight and gestational age decrease and these multiple complications or risk factors further increase the risk of neurodevelopmental disability (Leppert & Allen 2012; Pineda et al. 2013).

2.2.2 Defining 'high risk'

Leppert and Allen (2012, p.920) refer to high-risk as the 'likelihood of neurodevelopmental disability, which is a group of interrelated, chronic, non-progressive disorders of the central nervous system caused by injury to or malformation of the developing brain'. There are many different guidelines to follow when identifying infants who may be termed 'high-risk'. Common complications and risk factors can be grouped according to body structures and functions, namely; pulmonary conditions, neurologic conditions, cardiac conditions, organ dysfunctions and other medical conditions (Khan-D'Angelo et al. 2012). Leppert and Allen's (2012) categories of perinatal risk factors are more extensive and include background characteristics, prenatal and obstetric complications, physical characteristics, condition at birth, neonatal complications, and measures of central nervous system (CNS) structure and function.

2.2.3 NICU environmental stressors

When studying the neurodevelopment of neonates, one cannot ignore the effects of the NICU environment and the impact it may have on developing neonates. It is a well-known fact that neonates in NICU, particularly preterm infants, are very sensitive to touch, lighting changes and noise which have numerous effects on their physiological and neurological states, often compromising respiration (White 2011). Even though the highest priority in an

NICU is to save lives, an increasing amount of literature emphasises the impact that the stressful environment has on developing neonates. The first stressors to be investigated were noise and lighting (White, 2011). Following this were many studies investigating pain experiences in the NICU, with subsequent development of methods to measure pain and stress of infants (Gibbins & Stevens 2001; Newnham et al. 2009). Loud noises have been found to cause an increase in autonomic response in neonates potentially leading to bradycardia and hypoxic episodes. It is also agreed that bright lights adversely affect neonates particularly those born before 32 weeks gestational age, as they have thin eyelids and decreased ability to limit the amount of light entering the eyes (Khan-D'Angelo et al. 2012).

Studying a preterm infant's perception of pain is complex. Newnham et al. (2009) have described a lack of concordance between behavioural and physiological responses to pain, particularly at earlier gestational ages. But it is agreed that pain in this population can increase blood pressure, heart rate and intracranial pressure and decrease oxygen saturation (Newnham et al. 2009). Many studies have proposed that the bright and noisy environment adversely affects growth and development especially of the very preterm infant (Pineda et al. 2014). Infants in an NICU are exposed to this stressful environment at a critical time of CNS development and vulnerability, and there is increasing evidence that the repeated stressors have profound effects on several physiological systems, one being the CNS (Newnham et al. 2009).

2.3 The effects of common neonatal morbidies on neurodevelopment

2.3.1 Prematurity and low birth weights

Many complications encountered in an NICU are due to prematurity and low birth weights. There is extensive literature linking prematurity and it's effects to neurobehavioural changes and long-term neurodevelopmental difficulties (Khan-D'Angelo et al. 2012; Pineda et al. 2013). Low birth weight (LBW) is

defined as 1501-2500 grams, very low birth weight (VLBW) is defined as 1000-1500 grams, and extremely low birth weight (ELBW) as less than 1000 grams (Khan-D'Angelo et al. 2012). In a literature review by Jarjour (2015), it was found that extreme preterm (EP) infants (less than 25 weeks gestation) have a very low likelihood of surviving without impairment. The author reviewed 16 articles from a 14 year period, and looked at results from both short- and long-term follow-up. The review showed that nearly half of the surviving EP infants had significant neurodevelopmental disabilities at follow-up. The most frequently ocurring long-term complication was intelectual disability (Jarjour 2015).

2.3.2 Chronic lung disease

Chronic lung disease (CLD) and bronchopulmonary displasia (BPD) are two of the most common respiratory complications of preterm birth and are caused by incomplete or abnormal repair of lung tissue during the neonatal period (Khan-D'Angelo et al. 2012; Pfister & Goldsmith 2010; Poon et al. 2013). Embryologically, the lungs develop in five different stages, namely; embryonic, pseudoglandular, canalicular, saccular, and alveolar. Infants that are born at less than 28 weeks gestation have inefficient gas exchange and are at risk of disrupted or arrested alveolarisation as they are only at the late canalicular or early saccular stage (Bhakta & Stark 2006; Poon et al. 2013). Infants with CLD or BPD require supplemental oxygen and often require continued oxygen supplementaion after discharge from hospital in the form of 'home oxygen' (Khan-D'Angelo et al. 2012). Long-term consequences of CLD have been seen in childhood and through to adulthood (Poon et al. 2013). This group of infants generally have poorer neurodevelopmental outcomes compared to unaffected infants. The influence of CLD on development may be associated with poor nutrition and growth, feeding difficulties, prolonged hospitalisation and repeated nosocomial infections (Bhakta & Stark 2006; Khan-D'Angelo et al. 2012).

2.3.3 Periventricular leukomalacia and intraventricular haemorrhage

Among the many difficulties that preterm infants encounter, cerebral injury is a common morbidity and both cerebral injury and altered cerebral development can negatively influence neurodevelopment in these infants (Pineda et al. 2013; Vollmer et al. 2006). Cerebral injuries are often associated with suboptimal or abnormal neurodevelopmental outcome (Leijser et al. 2009). In particular, preterm infants are at risk of intraventricular haemorrhage (IVH) and periventricular haemorrhage (PVH), periventricular leukomalacia (PVL) and more diffuse white matter injury. Khan-D'Angelo et al. (2012) define PVL as a symmetrical, non-haemorrhagic usually bilateral lesion caused by ischaemia from alterations in arterial circulation. Leijser et al. (2009) refer to PVL as the predominant form of brain injury and the leading known cause of CP in preterm infants. There are many different factors that may cause the change in arterial circulation. It has been shown that lesions which form cysts are correlated with cerebral palsy (CP) and cognitive impairment, where larger and bilateral cysts present a higher risk (De Vries et al. 2004; Khan-D'Angelo et al. 2012).

PVL is often associated with IVH (Volpe 2001). Like various other risk factors, there is an inverse relationship between gestational age and IVH. Haemorrhage occurs from the primitive capillaries, and interferences with cerebral blood flow autoregulation increase the risk of vessel rupture. These disturbances can be caused by any neonatal event that may lead to change in cerebral blood flow, hypoxia or hypoxaemia. IVH can be classified from grades one to four, with grade four being the most severe (haemorrhage into the periventricular white matter). There is a greater incidence of neurodevelopmental problems in infants with severe haemorrhage ranging from CP and hydrocephalus to cognitive, sensory and learning disorders (Khan-D'Angelo et al. 2012).

2.3.4 Necrotising enterocolitis

Necrotising enterocolitis (NEC) is an acute inflammatory disease of the premature infant's bowel (Khan-D'Angelo et al. 2012). Several factors

predispose infants to NEC. It can be further classified into medical NEC and surgical NEC (Martin et al. 2010). The relationship between NEC and neurodevelopment is complex. NEC is not seen as the direct cause of poor neurodevelopment. In a study by Martin et al. (2010) they observed that increased severity of disease, i.e. surgical NEC, predisposed infants to adverse neurodevelopment. They explained that the injured gut contributes to a systemic inflammatory response which can affect the developing brain, and that NEC could be a marker for overall severity of illness during the NICU stay. NEC will also expose the infant to other risk factors, for example, anaesthesia during surgery. The study included 1155 infants and assessed neurodevelopment at 24 months corrected age using the Bayley Scales of Infant Development-Second edition (BSID-II). The authors concluded that infants who had surgical NEC were at higher risk for poor developmental outcomes compared to those who didn't (Martin et al. 2010). The risk of adverse neurodevelopment in infants with NEC has also been demonstrated in data collection done by allied health professionals at Chris Hani Baragwanath Hospital (CHBAH) in 2013. The third most common co-morbidity in the population was NEC, and it was associated with motor and cognitive delays (Bulmer 2014).

2.3.5 Neonatal jaundice

In the same data collected at CHBAH, neonatal jaundice (NNJ) was also found to be a co-morbidity in infants with suboptimal development in motor, communication and sensory domains. It was the most frequently occurring risk factor in the population (Bulmer 2014). NNJ or neonatal hyperbilirubinaemia, is defined as the accumulation of excessive amounts of bilirubin in the blood. It is a condition seen in both preterm and term neonates and has numerous causes. Hyperbilirubinaemia becomes dangerous to the developing brain if unconjugated bilirubin is deposited in the brain, known as kernicterus (Khan-D'Angelo et al. 2012). The part of the brain most affected by unconjugated bilirubin is the basal ganglia. In a small study by Gkoltsiou et al. (2008) seven out of eleven infants of varying gestational age, at risk of

kernicterus as neonates, were diagnosed with CP. Three of the seven infants with CP had dyskinetic or athetoid movements and four infants were severely dyskinetic. Despite the small sample size of 11, the study showed that 63.6% of the sample had severe neurological fallout. Mukhopadhyay et al. (2010, p. 333) re-iterate in their study that 'the association between a high bilirubin level and brain damage is well-established', therefore early and effective treatment of NNJ is paramount in preventing kernicterus and subsequent adverse neurodevelopment.

2.3.6 Neonatal sepsis

Neonates are at risk of multiple infections during hospitalisation (Mitha et al. 2013). Sepsis may harm the developing brain and lead to neurological complications such as PVL and ultimately poor neurodevelopmental outcomes (Schlapbach et al. 2011). In a large, well-conducted cohort study on extremely preterm infants, Schlapbach et al. (2011) showed that sepsis independently increased the risk for adverse neurodevelopment. In this study, 541 participants were included and neurodevelopmental assessments were carried out using the BSID-II at 24 months corrected age. Infants with infection were compared to uninfected infants. Ten percent of infants with proven sepsis were diagnosed with CP. In a very large cohort study conducted by Mitha et al. (2013) it was found that infections in preterm infants were associated with a higher risk of CP, compared to uninfected infants. The study included 2277 infants with various confirmed pathogens and assessed long-term neurodevelopment at five years. The frequency of CP was 9% and that of intellectual impairment was 12%. They found this result to be consistent with the neurotoxic effects of infectious or inflammatory mediators on cerebral white matter (Mitha et al. 2013). In contrast to the study by Schlapbach et al. (2011), this study did not account for other comorbidities that might have been experienced.

2.4 Term graduates

Historically, there is little literature discussing full-term NICU graduates, particularly their long-term neurodevelopment. However, a significant number are admitted to NICU's. Term infants may not attend a follow-up service regularly, as they may not have had the plethora of complications that a preterm infant might have had, yet their conditions are also grave enough to warrant NICU admission. Late preterm (33-36 weeks gestation) and early-term (37-39 weeks gestation) infants are two additional groups that are not given as much attention as extreme preterms. Recent literature has highlighted sub-optimal long-term developmental outcomes in these two groups of neonates (Romeo et al. 2010; Dong et al. 2012).

Term infants are commonly admitted to the NICU for perinatal asphyxia, birth trauma, congenital syndromes, congenital pneumonia, or sepsis (Schiariti et al. 2008). Although they have a greater weight and, for the most part, fully developed body systems, term infants are still at risk of being affected by the adversities encountered in the NICU.

2.5 Follow up and early intervention

Literature suggests that all high-risk infants should attend a comprehensive follow up programme to provide interventions early on (Hilderman & Harris 2014). During follow up at a medical centre, a multidisciplinary team can identify problems or concerns, either medical or neurodevelopmental (Greene et al. 2013). It is the ideal setting for early intervention. Early intervention aims to improve functional outcomes by screening a high-risk population and coordinating therapeutic services (Litt & Perrin 2014). It spans many areas of therapy and is a broad term used to describe the timely assessment and treatment of individuals with or at risk of any kind of disability, at any age. In this case, early intervention for the purpose of developmental screening of high-risk infants, can be termed 'early childhood intervention' (ECI). The definition used for ECI in infants at risk for developmental disabilities, as quoted by Shonkoff and Meisels in Blauw-Hospers and Hadders-Algra (2005, p. 421) is as follows; 'Early Intervention consists of multidisciplinary services

provided to children from birth to 5 years of age to promote child health and well-being, enhance emerging competencies, minimize developmental delays, remediate existing or emerging disabilities, prevent functional deterioration, and promote adaptive parenting and overall family functioning. These goals are accomplished by individualized developmental, educational, and therapeutic services for children provided in conjunction with mutually planned support for their families'

The age at which to begin ECI in this population is debatable, and largely depends on the condition of the child, whether a developmental disorder is already apparent or not yet clear. Different interventions may start as early as in the NICU, post-NICU discharge up to nine months, and from nine months to 18 months as reported in a systematic review of 34 studies by Blauw-Hospers & Hadders-Algra (2005). The evidence for the preferred initiation period is inconclusive, but benefits are reported for all stages. There is also no conclusive evidence as to which physiotherapy techniques are preferred but it is widely suggested that programs be individualised according to a child's age, needs and abilities (Blauw-Hospers & Hadders-Algra 2005; Fernandez et al. 2012; Spittle et al. 2012).

Primarily, the physiotherapist's focus in ECI is motor function however, all disciplines of therapists are encouraged to assess and integrate all facets of a child's development (Hilderman & Harris 2014). This includes considering a child's environment, family and socio-economic situation. Possibly the most important part of ECI is parent or caregiver education and empowerment, in order to facilitate carry-over of skills into daily life (Vanderveen et al. 2009).

In 2012, a Cochrane review was done by Spittle et al. (2012) with the aim of reviewing the effectiveness of early developmental intervention on motor and cognitive development. Twenty-one randomised or quasi-randomised controlled trials involving 3133 infants were included. The studies compared

effects of early developmental intervention programmes post-hospital discharge, to standard medical follow-up. All infants had gestational ages of less than 37 weeks. Results of the effects on motor and cognitive development were analysed in age groups, namely; infancy (zero to two years), pre-school age (three to less than five years), school ages (five to 17 years) and adulthood. The analysis demonstrated that early developmental intervention had a significant positive effect on cognitive development at infancy and pre-school age, and a small effect on motor development only at infant age. No substantial long-term outcomes were shown in this review (Spittle et al. 2012). The interventions that were included were not able to prevent cerebral palsy or other neuro-motor impairments in a number of infants, but may have an effect on the functional outcomes of the disorders (Hilderman & Harris 2014).

2.6 Neurodevelopment in a developing country

There are a great many factors that influence a healthy infant's neurodevelopment in low- and middle-income countries worldwide. It is estimated that nearly 200 million children do not reach their developmental potential (Sabanathan et al. 2015). When assessing the neurodevelopment of healthy or at-risk infants in a country such as South Africa, it is important to consider the factors that may influence developmental potential. Poverty, infectious diseases, and malnutrition including maternal malnutrition have been found to have long-term detrimental effects on infant development (Kerac et al. 2014; Sabanathan et al. 2015) . Low maternal education level and parental stress due to low socio-economic status may lead to inadequate cognitive stimulation of infants in the household (Wehby & McCarthy 2013). Koutra et al. (2013) conducted a large cohort study which used self-reported measures by mothers and neurodevelopmental assessments of their infants at 18 months using The Bayley Scales of Infant and Toddler Development-Third edition (Bayley-III). The authors found that maternal post-partum stress and depression may have negative effects on maternal involvement with the infant, putting the infant at risk of delayed cognitive development. Studies

have shown that parent-infant interactions may be compromised in families whose infants are NICU survivors, due to the prolonged parent-infant separation and perceived 'caregiving from a distance' as well as parental emotional stress (Vanderveen et al. 2009).

2.7 Human Immunodeficiency Virus

In 2002, prevention of mother-to-child transmission (PMTCT) was initiated in South Africa to reduce the risk of vertical transmission of the human immunodeficiency virus (HIV) from infected mothers to their infants (Coetzee et al. 2005; Sprague et al. 2011) . The progress made in PMTCT programmes has led to the virtual elimination of paediatric HIV in Europe and the United States (Ciaranello et al. 2012). In certain areas in South Africa, breast feeding is still encouraged for adequate infant nutrition. Even so, rates of mother-to-child transmission are between one and five percent, reaching the goal for 2015 set by the Joint United Nations programme on HIV/AIDS (Ciaranello et al. 2012; Ghanotakis et al. 2012).

HIV has been shown to have an adverse effect on paediatric neurodevelopment, particularly in infants who are not on highly-active antiretroviral therapy (HAART) (Hilburn et al. 2011; Potterton et al. 2010; Whitehead et al. 2013). In the vertical transmission of HIV, infection may occur in an infant's central nervous system during its early development (Hilburn et al. 2011). A study by Whitehead, Potterton and Coovadia (2013) compared the neurodevelopment of 27 HIV-infected infants and 29 HIV-exposed and uninfected infants. The results showed that HIV-infected infants scored lower on all scales of the *Bayley Scales of Infant and Toddler Development Third edition* (Bayley-III) compared to HIV-exposed and uninfected infants. These differences were seen from as young as four months of age.

There is little literature on the effects of maternal antiretroviral therapy (ART) on the developing foetal CNS. A large cohort study of 1869 births by Watts et al. (2013) showed that exposure to protease inhibitor-based combination ART in the first trimester was associated with preterm birth and spontaneous preterm birth. Of course, it is accepted that preterm birth may occur in this population due to many other factors including advanced disease, immune response and inflammatory mediators (Watts et al. 2013).

2.8.1 The Bayley Scales of Infant and Toddler Development

When assessing an infant's development there are many standardised assessment tools available, many of which are not validated for use in under-resourced settings in a developing country. The most widely used standardised and norm-referenced tool is the *Bayley Scales of Infant Development* (BSID) (Whitehead et al. 2014). It is a set of developmental scales designed to measure developmental functioning (Lennon et al. 2008). Nancy Bayley released the first commercially available version of the BSID in 1969 (Lennon et al. 2008). In 1993, the second edition (BSID-II) was published, and the third edition, differently named the *Bayley Scales of Infant and Toddler Development* (Bayley-III) was published in 2006 (Lennon et al. 2008; Piñon 2010).

The Bayley-III now includes a language scale together with the cognitive and motor scales, as well as subscales comprised of receptive language and expressive language, and fine motor and gross motor subscales (Greene et al. 2013). The normative data are representative of the infant population in the USA, between the ages of one month and 42 months. This sample was stratified on demographic variables that include geographic location, age, sex, and parent education level (Greene et al. 2013; Piñon 2010). In contrast to the previous Bayley scales, the Bayley-III normative data includes infants with various developmental conditions or risk factors. These special groups make up approximately ten percent of the normative data, and include children with cerebral palsy and children with Down syndrome, as well as various neonatal

risk factors such as birth asphyxia and prematurity (Crais 2010; Lennon et al. 2008; Piñon 2010). The Bayley-III is found to be both reliable and valid. Inter-rater reliability, test-retest reliability, and internal consistency were examined for reliability. Internal consistency of subscales and relationship with other outcome measures were evaluated for validity (Greene et al. 2013; Piñon 2010)

2.8.2 The Bayley-III Cognitive Scale

This first scale comprises 91 items which are aligned with recent developmental research on cognitive functioning (Armstrong & Agazzi 2010). Items assessing attention, habituation, memory, and conceptual reasoning were added to this scale to address information processing. Problem-solving, processing speed and early play skills were also researched for use in this scale (Armstrong & Agazzi 2010).

2.8.3 The Bayley-III Language Scale

The Bayley-III language scale looks at language and its related skills in the two subscales, receptive and expressive communication. Some areas have been expanded on and include pre-linguistic, social and complex language components (Crais 2010). It is important to note that the term *communication* indicates any means or combination of means that a child may use to interact with another person. This is especially noted in the early development of communication during the pre-linguistic stage, where children use gestures, facial expressions, vocalisations or eye gaze as forms of communication (Crais 2010).

2.8.4 The Bayley-III Motor Scale

The motor scale is divided into fine motor and gross motor subscales. The fine motor subscale evaluates specific skills that look at how effectively a child is able to use their hands to manipulate objects, use tools and play with toys

(Case-Smith & Alexander 2010). In particular this subscale assesses early hand and finger movement, reaching and grasping patterns, bimanual coordination, and the functional use of objects (Case-Smith & Alexander 2010).

The gross motor subscale assesses a child's performance of specific gross motor and locomotion tasks that are essential for mobility and play. This scale comprises skills incorporating early movement, postural stability and control, and balance and locomotion (Case-Smith & Alexander 2010). The variability in acquiring motor skills is vast, and many factors need to be considered. Many items in these subscales allow demonstration of a task before it is carried out, therefore considering possible limitations in exposure to a task.

2.9 Conclusion of literature review

A study of the literature shows that infants admitted to an NICU are exposed to many adverse events and due to their fragile nature, immature vital organs and immune systems they are predisposed to many diseases of the new-born and infections. These complications put the infants at risk of disrupted neurodevelopment and many studies presented in this literature review confirm the detrimental effects on long-term neurodevelopment. The need for identification of the infants who are most at risk and the importance of initiating early intervention strategies is highlighted in this review.

Chapter 3: **Methodology**

In this chapter the methodology used to conduct this study will be presented.

3.1 Location and population

The study was conducted at Chris Hani Baragwanath Academic Hospital, Soweto, Gauteng, South Africa. Infants with their caregivers attended the Neonatal Follow Up Clinic (NNFUC) where screening of NICU graduates was performed to identify eligible participants.

3.2 Ethical clearance

Prior to commencing data collection for this study, ethical clearance was obtained from the Committee for Research on Human Subjects of the University of the Witwatersrand (No. M140865 - see appendix). Permission was granted by CHBAH to conduct the research in the hospital's NNFUC. Participants were accompanied by one caregiver. Informed written consent was obtained from the caregiver of each participant. There was no need in any case for the informed consent to be translated. All information and records collected from participants were used solely for the purpose of this study, and are kept confidential. Privacy of participants was respected in a closed room. Participants who were found to have any neurodevelopmental fallout were referred to appropriate allied disciplines or multidisciplinary clinics.

3.3 Study Design

This is a cross-sectional observational study.

3.4 Inclusion Criteria

Infants who graduated from the NICU at CHBAH.

3.5 Exclusion Criteria

Infants diagnosed with Hypoxic Ischaemic Encephalopathy (HIE) II and HIE III were excluded, as they attend a different follow up clinic. Infants who were admitted only to the Neonatal Theatre unit were excluded as they attend a different follow up clinic.

3.6 Study sample

Unit statistics were used to calculate a study sample. In 2012 there were a total of 699 babies admitted to the NICU at CHBAH, giving a mean of 58 babies admitted monthly. Based on a population of 700 babies a year with a confidence interval of 15 and a 95 percent confidence level, a sample of 40 participants was needed for this study. Participants were of similar socio-economic status and cultural backgrounds.

3.7 Measurement tools

Developmental assessment tool: *Bayley Scales of Infant and Toddler Development Third edition*

Weight: The *SECA* infant weighing scale

Length: The *SECA* infant measuring board

Head circumference: Standard measuring tape

Clinical data: Data sheet

3.8 Procedure

Participants were screened at the NNFUC once a week. If their corrected age was between three and seven months, and they met the inclusion criteria, the caregiver was invited to participate. This was their regular follow up appointment therefore there were no extra transport costs for caregivers.

Caregivers attending the clinic with their baby were given an information sheet explaining the research study and assessment. If they agreed to their baby participating in the study, they were given a consent form to sign. The participant and caregiver were invited into a separate room where privacy was respected.

Participants were assigned study codes (numbers 1-40). The developmental assessment was carried out by the primary researcher prior to obtaining the demographic data, so as to minimise bias. The only information known to the researcher while conducting the assessment was the participants' corrected age.

A neurodevelopmental assessment was carried out for each participant, using the *Bayley Scales of Infant and Toddler Development* (*Bayley-III*). The assessment tool was explained to the caregiver beforehand. Each scale, namely cognition, language and motor, was administered to participants. In cases where participants were born preterm, the participant's age was corrected using 40 weeks gestation as the full term reference. Standard scores are derived by referring to the norms table appropriate for the adjusted age (Lennon et al. 2008). The researcher conducted all the assessments and has been trained in the use of the Bayley-III. The results for each scale were recorded on the outcomes form. Raw scores obtained from each participant were converted to scaled scores, and scaled scores for each domain were converted to composite scores.

All birth history, demographic and clinical data were collected from the participants' hospital file and recorded on the history form, once the neurodevelopmental assessment was complete.

Weight was measured by the clinic nurse on arrival at the clinic, and obtained from the hospital file by the researcher. Length and head circumference were measured by the researcher, after the neurodevelopmental assessment was complete, and recorded on the history form.

All participant information was kept in a filing system and kept confidential.

3.9 Statistical Analysis

Descriptive statistics e.g. mean and standard deviations (SD) were used to describe the demographic characteristics of the population. Percentages were used to summarise the medical histories of the participants.

The scores from the *Bayley-III* are presented as means and standard deviations.

Non-parametric tests such as the Chi-squared test were used to determine whether there are any relationships between demographic and clinical data and the Bayley-III composite scores.

Scores of the Bayley-III are interpreted as follows (Bayley, 2006):

Qualitative descriptions of composite scores from each domain

130 and above	Very Superior
120-129	Superior
110-119	High Average
90-109	Average
80-89	Low average
70-79	Borderline
69 and below	Extremely low

The results obtained in this study will be presented in chapter four.

Chapter 4: **Results**

The data from 40 participants were analysed.

4.1 Demographic data

The demographic data of the 40 participants is described in table 4.1. It is presented as means and standard deviations.

Table 4.1: Demographic data

Variable	**Mean (SD)**
Gestational age (weeks)	34 (5)
Corrected age (days)	147 (38)
Birth weight (grams)	2056 (852)
Current weight (grams)	6171 (1424)
Current length (cm)	60 (4)
Head circumference (cm)	40 (3)
Maternal age (years)	28 (7)
Apgar 1minute	6 (3)
Apgar 5 minute	8 (2)
Length of ICU stay (days)	20 (26)
Length of O2 dependence (days)	42 (52)

This table shows that the lowest birth weight was 810 grams and lowest gestational age was 26 weeks. The mean length of stay in NICU was 20 days, the longest stay in NICU was 135 days, or four months and 15 days. Length of oxygen dependency surpassed NICU stay, with a mean of 42 days and the participant who had the longest duration of oxygen dependency required supplemental oxygen for 244 days (eight months and four days). This was the participant's age at the time of the assessment. The participant was one of two who were oxygen dependent at the time of assessment. They

wore nasal cannulae connected to oxygen tanks. The mean corrected age of participants at the time of assessment was 147 days, or four months and 27 days.

Z-scores were calculated for all participants using weight-for-age and length-for-age. This was done using the corrected age of each participant. Five participants (12.5%) had a Z-score of below minus 3 for weight, and nine participants (22.5%) had a Z-score of below minus 3 for length.

Table 4.2 presents demographic data of the participants that cannot be presented as means, but as frequencies.

Table 4.2: Demographic data as percentage

Variable	Percentage (%)
Male	50.0
Female	50.0
Caesarean section	52.5
NVD	47.5
Mother ARV's	32.5
Mother alcohol	2.5
Mother steroids	2.5

There were an equal number of male and female participants. The number of participants born by normal vaginal delivery (NVD) and caesarean section were almost equal with a difference of two participants. All 40 participants were of the same ethnicity (black). One participant's mother drank alcohol during the pregnancy, one mother was given steroids prior to delivery, and 13 mothers were taking ARV's during the pregnancy.

Table 4.3 describes the types of ventilation or oxygen delivery that participants required during their NICU admission.

Table 4.3: Modes of ventilation

Ventilati	Percentage (%)
IPPV	90.0
NPO_2	72.5
NCPAP	57.5
HFOV	10.0

All 40 participants required one or more forms of ventilation. The most frequent type of ventilation used was intermittent positive pressure ventilation (IPPV) with 36 participants (90%) requiring this. Only 10% of participants were put onto high frequency oscillatory ventilation (HFOV). Nasal prongs oxygen (NPO_2) delivered via cannula, and nasal continuous positive airway pressure (NCPAP) were used in 72.5% and 57.5% of participants respectively; a large proportion.

4.2 Medical complications during admission

Table 4.4 documents the variety of conditions that the participants presented with in the study. They are tabulated according to percentage of the population affected.

Table 4.4: Conditions as percentage

Condition	%	Condition	%
Sepsis	67.5	Periventricular Leukomalacia	20.0
Blood transfusion	55.0	Meconium Aspiration Syndrome	15.0
Neonatal Jaundice	37.5	Multiple pregnancy	12.5
Hyaline Membrane Disease	37.5	Hypotension	12.5
Retroviral Disease exposed	32.5	Hyperglycaemia	10.0
Chronic Lung Disease	30.0	Seizures	10.0
Anaemia	30.0	Surgical NEC	7.5
Patent Ductus Arteriosis	27.5	Hypoxic Ischaemic Encephalopathy I	7.5
Necrotising Enterocolitis	25.0	Thrombocytopaenia	5.0
Intraventricular Haemorrhage	22.5	Retinopathy of Prematurity	5.0
Respiratory Distress Syndrome	22.5	Retroviral Disease positive	2.5
Pneumonia	20.0	Neonatal Encephalopathy	2.5

All participants had one or more of the complications listed in table 4.4. The highest number of comorbidities experienced by a single participant during NICU admission was 12. The number of comorbidities decreased with increasing birth weight. IVH and NEC were associated with preterm birth less than 32 weeks gestation. The multiple pregnancies were all twin births and only one twin from each set was admitted to NICU and therefore assessed in the study. All twin pregnancies were associated with preterm birth of less than 34 weeks gestational age.

The table shows that 13 participants (32.5%) were exposed to HIV (retroviral disease exposed). All 13 mothers of these participants were taking ARV's or initiated ARV's during their pregnancy. All 13 participants were given Nevirapine for 6 weeks post-delivery. Only one participant tested positive for HIV.

4.3 Medical complications - specific

4.3.1 Genetic conditions

Genetic conditions or malformations were diagnosed in six participants (12.5%). These included gastroschisis, coanal atresia, micrognathia, cribriform plate haemangioma, unspecified dysmorphism, and mosaic Down syndrome.

4.3.2 Neurological conditions

Neurological conditions were present in nine participants (22.5%). Neurology included seizures, dilated ventricles, cerebral palsy, unspecified hypertonia and jitteriness, arrested hydrocephalus, microcephaly, cerebral infarcts and atrophy, and meningitis

4.3.3 Surgery during admission

Surgical procedures were performed on nine participants (22.5%). Types of surgery included staged gastroschisis closure, NEC repair, laporotomy and colostomy, PDA closure, pencil drain insertion, diaphragmatic hernia repair, insertion of nasal stents, duodenal atresia repair, cardiac surgery for ventriculo-septal defect, coanoplasty. Two participants underwent more than one surgical procedure.

4.4 Pathogens found in septic participants

Episodes of sepsis occurred in 27 participants (67.5%) during NICU admission. The following table, table 4.5, describes the types of pathogens that were discovered on blood test cultures and the percentage of participants that they occurred in. In some instances, participants were diagnosed with more than one pathogen during admission.

Table 4.5: Pathogens as percentage

Pathogen	Percentage (%)
Unspecified sepsis	25.0
Methicillin-resistant Staphylococcus Aureus (MRSA)	12.5
Acinetobacter Baumanii	12.5
Klebsiella	10.0
Staphylococcus Aureus	7.5
Fungal (unspecified)	7.5
Candida Albicans	7.5
Enterobacter cloacae	2.5
Tropicalis	2.5
Escherichia coli	2.5
Enterococcus faecalis	2.5
Candida parapsilosis	2.5
Group F streptococcus	2.5

Methicillin-resistant staphylococcus aureus (MRSA) and Acinetobacter baumanii are equally the most commonly occurring pathogens in this study population. However, in a quarter of the population, the type of sepsis was not specified.

4.5 Interventions during admission

During NICU admission or post-NICU discharge many neonates undergo non-medical interventions and therapies to promote normal development, increase weight, improve feeding, maintain normal movements and postures, and education of parents. For this population, the different types of non-medical interventions that a portion of participants received are listed in the table below. Participants may have received only one intervention, or all.

Table 4.6: Non-medical interventions as percentage

Intervention	Percentage (%)
Speech Therapy	50.0
Physiotherapy	30.0
Kangaroo mother care (KMC)	5.0

Half of the participants in the study were treated by a speech therapist for difficulty with feeding or assisting with transitioning to oral feeding post-NICU discharge. A lower percentage (30%) of participants were treated by a physiotherapist. This could consist of developmental care or specific rehabilitation exercises, or chest physiotherapy. Only five percent of participants stayed in the KMC unit with their mothers.

4.6 Bayley-III scores

The scores of the neurodevelopmental assessment are presented in means and standard deviations (SD). The composite scores for each scale are presented in the graph and table below.

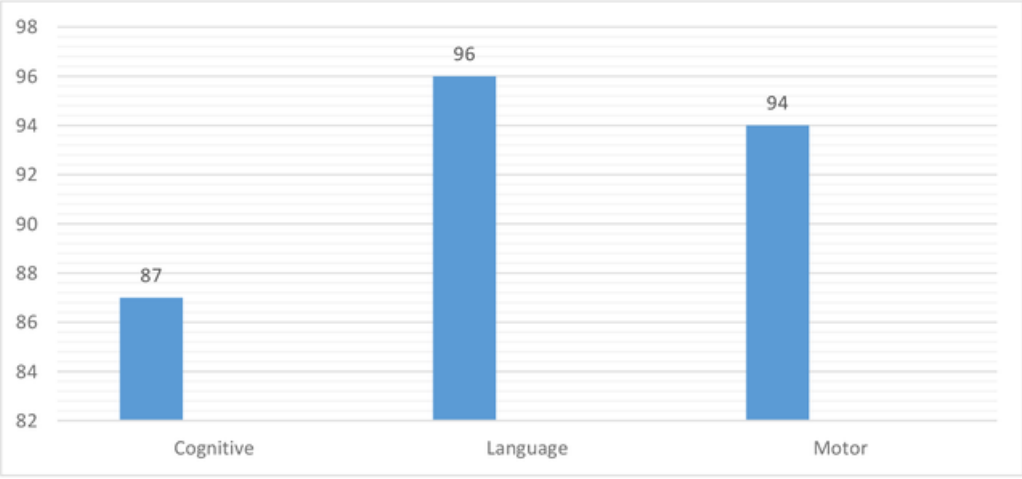


Figure 4.1: Composite scores

This graph illustrates that the cognitive scale has the lowest mean score of 87 (SD=16). The motor scale has a mean score of 94 (SD=11) and the language scale has the highest mean score of 96 (SD=22). All of these scores fall in the average and low average categories.

Table 4.7 presents the highest and lowest composite scores of each scale, namely; cognitive, language and motor.

Table 4.7: Highest and lowest composite scores

Scale	Highest score	Lowest score
Cognitive	120	55
Language	121	77
Motor	145	58

When assessing individual scale composite scores of 40 participants, Table 4.7 confirms that the cognitive scale has the lowest scores, with both the highest and lowest scores being lower than those of the language and motor scales. The motor scale boasts the highest score out of the three scales, however it is not the highest mean score. The lowest cognitive scores were found in participants with respiratory distress syndrome, twin birth, and genetic conditions. The highest motor scores were found in participants with birth weights greater than 3000 grams. The group of females had higher mean scores than the group of males, particularly in the cognitive scale.

The following figures are pie charts representative of each Bayley-III scale. Scoring categories are presented as percentages of the total and are colour-coded according to the key.

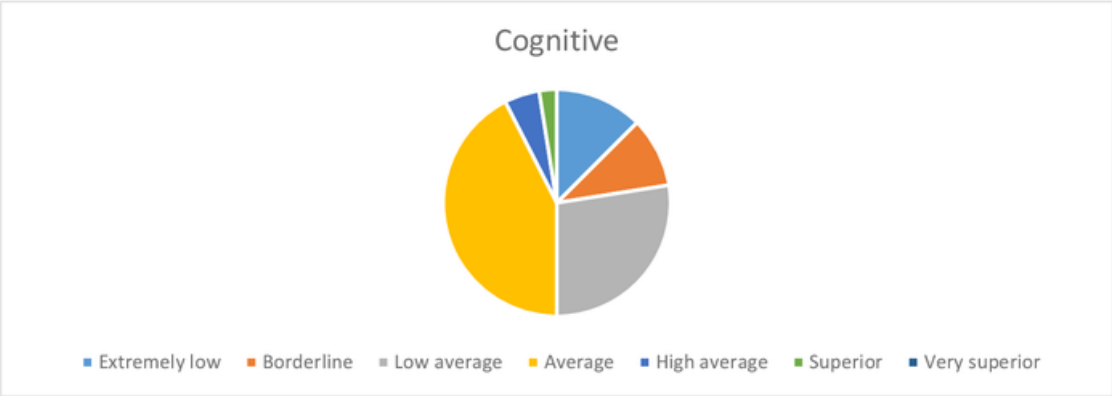


Figure 4.2: Cognitive descriptive groups

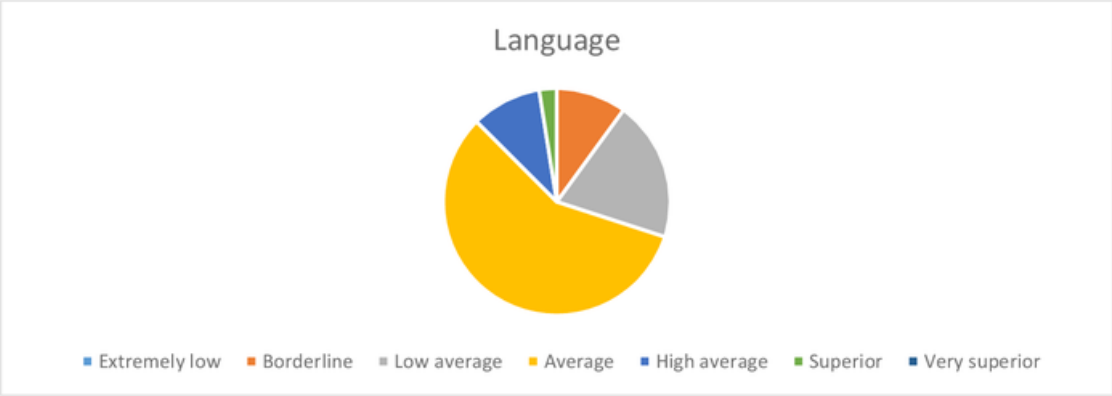


Figure 4.3: Language descriptive groups

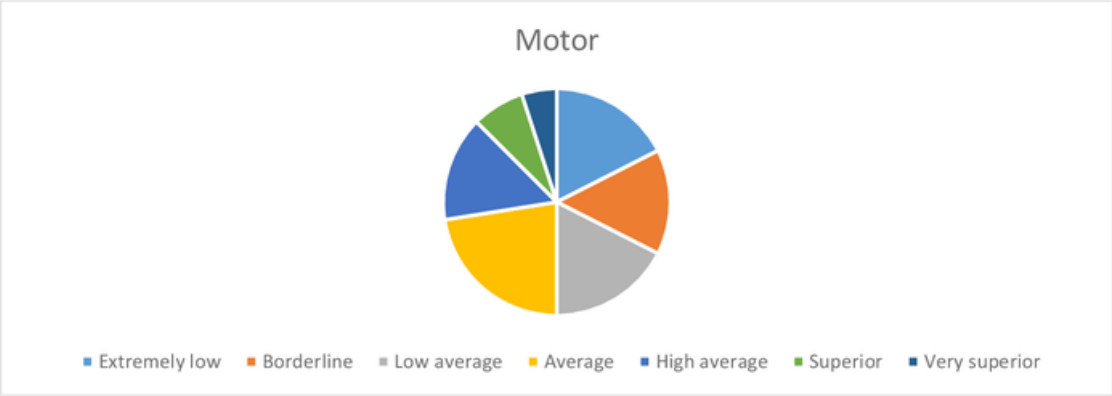


Figure 4.4: Motor descriptive groups

As evidenced by the pie charts, the motor scale has the most widely distributed scores with participants scoring in each category. It is the only scale with very superior participants, making up five percent of the total. The motor scale also has the highest percentage of extremely low scores, being 17.5%.

4.7 Descriptive analysis

Composite scores that were less than or equal to 85 were analysed for each subscale, for each medical complication. The data is presented in table 4.8 as frequencies.

Table 4.8: Frequency of complications in scores ≤85 (at risk) on each scale

Complication	Number on cognitive scale	%	Number on Language scale	%	Number on Motor scale	%
Male	12	60.0	3	15.0	11	55.0
Female	8	40.0	3	15.0	6	30.0
RVD exposed	6	46.1	1	7.6	6	46.1
NVD	12	63.1	4	21.0	12	63.1
Caesarian	8	38.0	2	9.5	5	23.8
IPPV	17	47.2	5	13.8	15	41.6
HFOV	1	25.0	0	0.0	1	25.0
CPAP	11	47.8	5	21.7	10	43.4
NPO_2	16	55.1	5	17.2	12	41.3
PDA	5	45.4	0	0.0	3	27.2
CLD	8	66.6	3	25.0	7	58.3
PVL	4	50.0	1	12.5	3	37.5
Sepsis	17	62.9	5	18.5	14	51.8
Twins	4	80.0	1	20.0	4	80.0

NNJ	8	53.3	3	20.0	10	66.6
NEC	6	60.0	2	20.0	7	70.0
NEC surgery	1	33.3	1	33.3	2	66.6
RDS	6	66.6	2	22.2	4	44.4
HMD	8	53.3	2	13.3	8	53.3
MAS	1	16.6	2	33.3	1	16.6
IVH	7	77.7	2	22.2	6	66.6
HIE I	1	33.3	0	0.0	1	33.3
T/F	13	59.0	4	18.1	11	50.0
Seizures	3	75.0	1	25.0	1	25.0
Anaemia	6	50.0	2	16.6	8	66.6
Hypotension	2	40.0	0	0.0	1	20.0
Hyperglycaemia	1	25.0	0	0.0	2	50.0
Thrombocytopaenia	1	50.0	0	0.0	1	50.0
Genetic abn.	4	66.6	1	16.6	3	50.0
Pneumonia	2	25.0	0	0.0	0	0.0
ROP	1	50.0	0	0.0	1	50.0
Neurology	6	66.6	1	11.1	3	33.3
Surgery other	5	55.5	2	22.2	5	55.5

The total number of participants in each scale who had scores less than or equal to 85; were 20, six and 17 on the cognitive, language and motor scales respectively. The participants are classified as 'at risk' for abnormal development by their low scores. The language scale has by far the lowest number of abnormal scores, corresponding to the information presented in point 4.6. This very low number accounts for the low percentages of complications found on this scale in table 4.8. On all three scales, in this low-scoring category, the mean gestational age was the same: 33 weeks. The mean birth weights were 1830 grams, 2118 grams and 1788 grams for the cognitive, language and motor scales respectively.

The most frequently occurring complication in this category was twin pregnancy, with 80% occurring in both the cognitive and motor scales. On the cognitive scale in this low-scoring category, the presence of IVH and seizures were frequent with 77.7% and 75% respectively. On the motor scale the next most frequently occurring complication was NEC with 70%.

4.8 Statistical analysis

The data collected in this study was analysed with the use of STATA. The Chi-squared test was used to investigate associations between scores indicating risk of abnormal development and participant characteristics and complications. With a 95% confidence interval, 5% as well as 10% levels of significance were used to show relationships and trends. The significant values are presented in table 4.9, table 4.10 and table 4.11.

Table 4.9 Statistically significant values for characteristics in the cognitive scale

Characteristic	P=0.05	P=0.1
Sepsis	P=0.018	
IVH		P=0.058
Birth weight		P=

Table 4.10 Statistically significant values for characteristics in the language scale

Characteristic	P=0.05	P=0.1
PDA		P=0.076
RDS		P=0.057

Table 4.11 Statistically significant values for characteristics in the motor scale

Characteristic	P=0.05	P=0.1
NVD	P=0.004	
Anaemia	P=0.038	

It was found that participants with sepsis during NICU admission were at risk of abnormal cognitive development (P=0.018) at a 5% level of significance. On the language scale, no characteristics were significant at P=0.05. Participants born via NVD (P=0.004) and those who experienced anaemia (P=0.038) during NICU admission were found to be at risk of abnormal motor development, at a 5% level of significance.

At a 10% level of significance, IVH (P=0.58) and birth weight (P) were associated with a risk of abnormal cognitive development. PDA (P=0.076) and RDS (P=0.057) were found to be risk factors for abnormal language development at a 10% level of significance.

Trends were discovered on the language and motor scales, with characteristics that were almost significant in terms of risk of abnormal neurodevelopment. These include NVD (P=0.112) on the language scale, and NNJ (P=0.102), NEC (P=0.144) and twin pregnancy (P=0.151) on the motor scale.

4.8 Participant profiles

4.8.1 Lowest overall scoring participants

The following two tables show the scores of the lowest scoring participants in the study.

Table 4.12: Score profile lowest scorer

Scale	Composite score	Classification
Cognitive	55	Extremely low
Language	77	Borderline
Motor	58	Extremely low

This participant had the lowest scores overall as presented in Table 4.12, and was diagnosed with Mosaic Down syndrome. A participant with similar scores had no genetic condition, but suffered many complications during NICU admission. The scores of this participant are shown in Table 4.13 below.

Table 4.13: Score profile low scorer

Scale	Composite score	Classification
Cognitive	55	Extremely low
Language	77	Borderline
Motor	61	Extremely low

4.8.2 Highest scoring participants

Presented below are the composite scores of three participants who had high scores on the Bayley-III scales in this study.

Table 4.14: High score profile #1

Scale	Composite score	Classification
Cognitive	105	Average
Language	112	High Average
Motor	145	Very superior

Table 4.15: High score profile #2

Scale	Composite score	Classification
Cognitive	110	High Average
Language	121	Superior
Motor	121	Superior

Table 4.16: High score profile #3

Scale	Composite score	Classification
Cognitive	120	Superior
Language	115	High Average
Motor	115	High average

The mean corrected age of the above three participants was four months and nine days at the time of the neurodevelopmental assessment.

In the following chapter, the findings of this study will be discussed.

Chapter 5: **Discussion**

The results presented in chapter 4 will be discussed in this chapter.

5.1 Results of Bayley-III neurodevelopmental assessments

5.1.1 Significance of the Bayley-III scores of this study sample

The mean language and motor composite scores of this study population were average (96 and 94 respectively), and the mean cognitive score was low average (87). There are many different definitions for developmental delay, and unanimously the definitions suggest that an infant must perform below, or worse, than their same-age peers on a developmental test for a diagnosis of developmental delay to be given. Although the Bayley-III neurodevelopmental assessment can provide relevant developmental age information interpreted as scores, it is highly recommended to assess the full clinical picture of an infant using more than one source of information before giving the diagnosis of developmental delay (Bayley 2006). On each scale of the Bayley-III an abnormal score (abnormal development) is stated as that below 70, and a score between 70 and 85 indicates risk of developmental delay (Ballot et al. 2012).

When compared to another South African study by Ballot et al. (2012), the scores of the current study are similar yet slightly higher. The study by Ballot et al. (2012) also performed the Bayley-III neurodevelopmental assessment on a comparable population group to the current study (neonatal unit survivors at follow-up) but had a study sample of 106 infants. The mean composite scores on the Bayley-III assessment were as follows; 89 on the cognitive scale (low average), 88 on the language scale (low average), and 90 on the motor scale (average). Compared to the current study, only the cognitive score is higher. However, in the study by Ballot et al. (2012), the median age at assessment was 16.48 months in contrast to the current study in which the mean corrected age was four months and 27 days. A similar study has not been found internationally as the studies involving NICU

survivors and using the Bayley-III have very specific inclusion criteria, too specific to be directly compared to the current study.

In the current study, five participants (12.5%) have cognitive scores lower than 70 classifying these participants as having abnormal development. On the motor scale, seven participants (17.5%) are classified with abnormal development (motor scores lower than 70). No participants have language scores lower than 70, therefore no participants in this study have abnormal development across all three subscales. In the 'at risk' category (scores between 70 and 85) on the cognitive scale there are 15 participants (37.5%), on the language scale there are six participants (15%), and on the motor scale there are ten participants (25%). Compared to the study by Ballot et al. (2012) where 15.1% of infants had abnormal development on one or more subscales, the results in the current study are similar. In that study, 3.7% of infants had abnormal development in all three areas, whereas the current study had none (Ballot et al. 2012).

With the Bayley-III, using the group classifications or levels of performance (from extremely low to very superior), can be useful when comparing the performance of an infant to that of an appropriate normative group. Performance on the Bayley-III can be analysed in terms of a participant's subscale score pattern (intraindividual perspective), or compared to an appropriate normative referenced group (interindividual perspective) (Bayley 2006).

The normative data for the updated Bayley-III were collected in the United States of America, over ten months in 2004. The sample was stratified on demographic variables including age and sex of infants, geographic location and education level of the parent. The normative group included infants with specific diagnoses and genetic conditions, these being; Down syndrome, CP, preterm birth, birth asphyxia, exposure to alcohol in utero and language

impairment, among others. This specific group made up ten percent of the total included in the normative group to ensure that it was representative of a population (Piñon 2010). The Bayley-III has been validated in many countries and across many socio-economic groups including South Africa.

5.1.2 Lowest overall scoring participants

The lowest scoring participant was diagnosed with Mosaic Down syndrome. In roughly two percent of Down syndrome cases, mosaicism on the trisomic cell line is seen, which means that the anomaly is found on only some cells and others are unaffected (Dreux et al. 2008). This participant had poor visual awareness. The comorbidities consisted of preterm birth (31 weeks), LBW, sepsis, NNJ, NEC, IVH and anaemia. The participant received rehabilitation services during hospital admission (post-NICU discharge). This participant's score profile is described in table 4.8 in chapter four.

The participant who scored the lowest overall without a genetic condition, had many comorbidities and stayed in NICU for over a month. This participant was born preterm at 32 weeks gestational age with a birth weight of 2645 grams. He is oxygen dependent and required supplemental 'home oxygen' at the time of assessment (total of 150 days). The participant's comorbidities consisted of CLD, PVL, sepsis, seizures, anaemia, cardiac surgery for a VSD, pulmonary atresia, and large, right-sided cerebral infarcts (posterior and middle cerebral artery regions). Importantly, this participant also had meningitis during admission and was later diagnosed with cerebral palsy, microcephaly and failure to thrive. There was one subsequent admission to hospital for poor feeding and bronchopneumonia. Table 4.9 in chapter four shows the scores of this participant.

5.1.3 Highest overall scoring participants

Three participants had equally high scores. The most comorbidities that occurred in any of these participants was four, with the mean number of comorbidities being two. All three participants only spent four days in NICU. Scores ranged from high-average to very superior. These participants were all above 32 weeks gestational age, and their birth weights were above 1700 grams.

5.2 Statistically significant associations

In the statistical analysis, using the Chi-squared test, various associations were found between risk of neurodevelopmental delay and patient characteristics or experienced complications. The small sample size must be taken into account when interpreting these data.

5.2.1 Sepsis and cognitive delay

Sepsis during NICU admission was significantly associated with risk of abnormal cognitive development (P=0.018). Sepsis was found to be the most frequent complication during NICU admission, occurring in 67.5% of participants. Sepsis may harm the developing brain and lead to neurological complications such as PVL and ultimately poor neurodevelopmental outcomes (Schlapbach et al. 2011). In a very large cohort study conducted by Mitha et al. (2013), infants who had various confirmed pathogens in the neonatal period were assessed at five years old. The results showed that the frequency of CP was 9% and that of intellectual impairment was 12%. They found this result to be consistent with the neurotoxic effects of infectious or inflammatory mediators on cerebral white matter (Mitha et al. 2013).

Preterm infants have a much higher risk (11 times greater) of infection compared to term infants, as their defence mechanism against infection is underdeveloped. Within the first three days of life, infection is classified as early-onset sepsis, and from four days of life it is classified as late-onset sepsis. Silva et al. (2015) conducted a prospective cohort study in an NICU in

Brazil, including 30 infants (mean gestational age of 28 weeks) and documented a number of characteristics. Forty-seven percent of infants in the study were diagnosed with late-onset sepsis. Risk factors for neonatal sepsis in this study were listed as immunological immaturity of the study population, mechanical ventilation, CPAP, and other invasive procedures such as central venous catheters (Silva et al. 2015). In comparison to the current study, the incidence of sepsis in the Brazilian study was lower. Ballot et al. (2012) also present a very low percentage of sepsis during hospital admission (13.3%) in their study of infants discharged from a neonatal unit, compared to the current study. However, the study included not only infants admitted to the NICU but also infants from the neonatal high care section and ward.

Infants in an NICU who have greater birth weight and gestational age are still at risk of late-onset sepsis (predominantly nosocomial sepsis) although to a lesser extent than LBW and preterm infants (Silva et al. 2015). In addition to this, there is a high turnover of infants in the NICU (596 admissions in 2014). There is also an extremely high number of births in the obstetric theatres and labour ward (20,137 live births in 2014), which are both operational for 24 hours a day, 365 days a year and are difficult to close down for disinfecting frequently (Nakwa 2015).

5.2.2 NVD and motor delay

Birth via NVD was found to be significantly associated with risk of abnormal motor development (P=0.004). At CHBAH the majority of pregnant women who attend the antenatal clinic are categorised as high risk, needing a tertiary level of care. Torabi et al. (2012) describe a high risk pregnancy as one in which the mother, foetus, or infant possibly encounter death, disability or disease. The most significant factors for these risks are preeclampsia, placental abruption, intrauterine growth restriction, maternal malnutrition and disease, pregnancy at the extremes of child-bearing age, and more than five previous pregnancies. At CHBAH, the deliveries that are deemed to be very high risk or doctors predict possible complications, are booked for Caesarean

section delivery. This is to minimise the complications that may arise for the infant and the mother. In essence, these infants are monitored perinatally owing to the known risk factors of the pregnancy or delivery. By delivering in a more controlled environment the risk of possible expected complications is lessened. In contrast to this, the majority of mothers delivering via normal vaginal delivery either have minimal or no risk factors and doctors deem an NVD to be safe, or deliver in an emergency before the scheduled date of delivery due to unforeseen complications. There is also a percentage of mothers who are not attending the antenatal clinic at CHBAH and have not been assessed for possible risk factors. These mothers usually present at their local clinic when they are in labour, complications are realised and they are referred to CHBAH for delivery and often give birth in the ambulance without a doctor or midwife. Others in this situation will choose to go straight to CHBAH if they are in the vicinity, and the delivery is not planned or prepared, leaving medical staff to deal with unpredicted complications. These explanations above could be the reason for NVD in this study population being a risk for abnormal motor development (P=0.004) as complications are unforeseen. In this study the percentage of preterm deliveries via NVD was 63.1%, confirming that these deliveries were unexpected and possibly proceeded without medical staff being fully prepared.

5.2.3 Anaemia and motor delay

Although blood transfusion is known to be associated with infectious and noninfectious risks, little is known about the long-term consequences of neonatal anaemia and its treatment (Widness 2008). Detrimental symptoms have been linked with anaemia in infants, such as tachycardia, poor weight gain, apnoea, and lactic acidosis (Valieva et al. 2009). Severe neonatal anaemia can impair cerebral oxygen supply, yet data on long-term outcomes following severe neonatal anaemia are scarce (Zonnenberg et al. 2016). In a study by Zonnenberg et al. (2016) MRI was performed on infants with severe anaemia. Results showed that some form of white matter injury was found in 64% of patients, as well as predominant patterns of injury in the basal ganglia and thalami. The infants were followed-up between 14 and 35 months of age

and neurodevelopment was assessed using the Griffiths Scale of Mental Development or the Bayley Scales of Infant Development. Outcomes of the tests were within the normal range for the majority of infants in the study (Zonnenberg et al. 2016).

In the current study, anaemia during NICU admission was significantly associated with abnormal motor development (P=0.038). The abovementioned effects that neonatal anaemia has on infants may serve as an explanation to the results found in this study.

5.3 Participant demographics and histories

5.3.1 Demographics of the population

At CHBAH, the minimum weight for admission into NICU is 1000 grams. If the infant's problems are purely respiratory, the NICU will accept an infant of 900 grams. There were two participants in this study with birth weights of less than 900 grams, who may have been admitted to NICU at a later stage (i.e. greater than 1000 grams) when complications arose.

The assessments were carried out over an eight month period, and corrected ages at the time of assessment varied greatly with a standard deviation of 38 days from the mean corrected age of 147 days. As the NNFUC is held weekly, caregivers often do not follow their given dates precisely and all the infants attending the clinic are of vastly different ages. Having an equal number of boys and girls was unintentional but is a good representation of infants attending the clinic. The maternal age was also over a wide range with three mothers of 17 years and two mothers of 39 years old, the mean maternal age being 28 years. This is comparative to the median maternal age found in the study also conducted in Gauteng by Ballot et al. (2012), which was 26 years (Ballot et al. 2012).

5.3.2 HIV

Almost one third (32.5%) of the participants in this study were exposed to HIV, which is comparable to 32.4% of infants who were exposed to HIV in a similar study conducted by Ballot et al. (Ballot et al. 2012). This is possibly due to similar characteristics of the mothers in each study attending similar hospitals, CHBAH and Charlotte Maxeke Johannesburg Academic Hospital (CMJAH). These two hospitals serve patients of largely the same socio-economic status, both in large cities in Gauteng.

Only one participant in this study's population had a positive HIV test. This participant's mother only initiated ARV's after five months of pregnancy. The HIV positive participant (three months and 23 days old at the time of assessment) was on combination ARV's consisting of 3TC (lamivudine), ABC (abacavir) and Kaletra (lopinovir/ritonavir). The gestational age and birth weight were in a normal range, 39 weeks and 2990 grams respectively. This participant did have a number of complications during and after NICU admission, however, the length of stay in NICU was only six days. The complications included; congenital pneumonia, hyperthyroidism, renal dysfunction, bilateral pneumothoraces, anaemia, hypotension, hypokalaemia and dermatological complications. The Bayley-III scores that this participant achieved were average (cognitive and language scales) and low average (motor scale).

5.3.3 Growth

The majority of participants in the study had weight-for-age and length-for-age values within normal limits (WHO 2008). Z-scores of below minus three for weight were documented in 12.5% of participants and Z-scores of below minus three for length were documented in 22.5% of participants in this study. A systematic review was conducted in South Africa reviewing the prevalence of stunting (length-for-age) of children less than six years of age (Said-Mohamed et al. 2015). Authors concluded that stunting still persists in the country at a significant level, despite economic transition over the past 40 years (Said-Mohamed et al. 2015).

5.3.4 Non-medical interventions

The CHBAH NICU does not practise Kangaroo Mother Care (KMC), however in the step-down wards it is part of a patient's management where appropriate. The aim of KMC in the CHBAH neonatal wards is largely promotion of weight gain and infants must be deemed medically stable. This may account for the low percentage (5%) of participants in this study who partook in KMC as most of the participant's medical recoveries were long and it is likely that their weight was sufficient by the time they were stable.

Infants in the neonatal unit are treated by speech therapy and physiotherapy on a referral basis, and there are always more infants in need of feeding assessments post-NICU discharge than infants in need of a musculoskeletal or neurological assessment. This is because during the critical post-NICU period, management is still aimed at "life-saving" rather than rehabilitation. Once infants are physiologically stable they can be referred to physiotherapy if it is needed, yet due to the high number of infants, medical staff tend to refer to physiotherapy if there is an obvious abnormality or neurological fallout and not necessarily for early developmental screening. Hence, at the NNFUC visits it is vitally important to screen these infants for developmental delay.

5.3.5 Longest NICU admission

The participant with the longest admission in NICU spent 135 days there (four months and 15 days). The participant was still oxygen dependent and was on 'home-oxygen' at the time of assessment. This participant was born preterm at 27 weeks gestational age with a very low birth weight (1030 grams). There were a total of eight comorbidities diagnosed which included CLD, PDA, PVL, surgical NEC, sepsis, IVH, hyperglycaemia, and HMD. This participant had average cognitive and language scores, and a borderline motor score due to poor endurance during motor activities. The effects of CLD and supplemental oxygen dependency have been documented in other studies, and shown to

have detrimental effects on neurodevelopment (Bhakta & Stark 2006; Khan-D'Angelo et al. 2012). Of note particularly is a study by Jones et al. (1995) in which a large cohort of oxygen-dependent neonates were assessed at three years of age. The results of a neurodevelopmental test showed that 35% of the population were severely disabled and 19% were diagnosed with cerebral palsy. The mean gestational age and birth weight were also low, 27 weeks and 1000 grams respectively (Jones et al. 1995)

5.4 Other frequent comorbidities and complications

5.4.1 Blood transfusions

There was a high number of blood transfusions needed in this population (55%). However only 54.5% of the transfusions were for anaemia, with no reasons given for the remaining 45.5%. Only two participants (five percent of the total) were diagnosed with thrombocytopaenia. This is an uncharacteristically low number for a population of neonates and perhaps in some cases, may not have formed part of the formal list of comorbidities due to the frequency of low platelet counts with each case. Many participants had more than one blood transfusion during their NICU admission.

Valieva et al. (2009) report on the effects of blood transfusions in neonates, in their retrospective study of 60 extremely low birth weight (ELBW) infants. The incidence of blood transfusions in the study population was 78%, considerably higher than the current study. The results showed an association between blood transfusions and BPD, NEC and diuretic use ($P<.05$) (Valieva et al. 2009). In contrast, the current study had a higher percentage of blood transfusions than the South African study by Ballot et al. (2012) which had a sample of 106 infants, where the percentage of blood transfusions was 30.2%.

5.4.2 Neonatal jaundice

NNJ, or hyperbilirubinaemia, was diagnosed in 37.5% of participants, and is a well-documented complication in neonates (Khan-D'Angelo et al. 2012). The mean birth weight in this group was 1649 grams and mean gestational age was 32 weeks. All infants were treated with phototherapy and recovered timeously, with no cases advancing to kernicterus thus not directly causing abnormal neurodevelopment in this population.

In the Netherlands, a stratified cohort of 832 neonates (gestational ages between 32 and 35 weeks) was analysed (Kerstjens et al. 2012). Associations between neonatal morbidities and developmental delay were assessed. In the study, the incidence of neonatal hyperbilirubinaemia was 46.4%, slightly higher than the current study. Hyperbilirubinaemia was not associated with developmental delay in the study (Kerstjens et al. 2012).

5.4.3 Hyaline membrane disease

In this study, 37.5% of infants were diagnosed with HMD. Included in this group, was the participant with the longest oxygen dependency. The mean length of supplemental oxygen in participants with HMD was 41 days, with a standard deviation of 61 days. Interestingly, also included in this group were the two participants who were diagnosed with ROP. ROP is known to be associated with the need for increased fractions of inspired oxygen, and all neonates requiring supplemental oxygen at CHBAH are screened for ROP (Khan-D'Angelo et al. 2012). Similarly to the NNJ group, the group with HMD had a mean gestational age of 32 weeks and mean birth weight of 1642 grams.

5.4.4 Hypoxic ischaemic encephalopathy and neonatal encephalopathy

In this study population, three participants were diagnosed with HIE I (seven point five percent). All three were born at full term, 40 weeks gestational age or more. Only one participant with HIE I had low scores on the Bayley-III

neurodevelopmental assessment. HIE I is the mildest form of HIE and usually results in very few complications (Robertson & Perlman 2006).

One participant was diagnosed with neonatal encephalopathy which was complicated by seizures, however, apgar scores were nine and ten for one and five minutes respectively. This participant's gestational age was 39 weeks, and only motor scores on the Bayley-III neurodevelopmental assessment were below average. The cause of neonatal encephalopathy is often unknown (The American College of Obstetricians and Gynecologists 2014).

5.4.5 Musculoskeletal complications

One participant had a femur fracture at the time of assessment (six months and 27 days corrected age). A family member had fallen onto the infant while carrying them. There was no associated head injury, and the fracture was being managed conservatively in a plaster of paris cast. This participant had low scores on the Bayley-III neurodevelopmental assessment, however also had a plethora of complications during the NICU admission.

5.5 Implications of the study

From the results obtained in this study it is evident that there are many complications which may be experienced during admission to an NICU. Coupled with the effects of the harsh environment, these complications may put an infant at risk for developmental delay or abnormal development. The mean neurodevelopmental assessment scores in this population were not favourable, showing low average or average performance. As shown, it is imperative for this high-risk population of infants to attend a follow up service where their neurodevelopment can be assessed by a therapist. In cases where intervention is necessary, it can be initiated during these follow up visits and further planning of therapy services can be done together with the caregiver.

Of importance, is the duration of stay in NICU and even more so, the duration of oxygen dependency. If not screened timeously, allowing early intervention to commence, these infants are at high risk for delayed neurodevelopment in one or more areas. The number of complications encountered by an infant is also a 'red-flag' for early detection and intervention, with higher numbers of complications putting infants at a greater risk for adverse neurodevelopment.

It is clear from the results of this study that infants who are diagnosed with a genetic condition or congenital abnormality should be assessed as soon as possible for neurodevelopmental delay. A clear therapy plan should be discussed with the family and intervention should start immediately.

All infants with known neurological conditions or neurological fallout of different causes should be assessed by a therapist for neurodevelopmental delay, as shown in this study. It is also recommended that infants who have undergone major surgery, attend a follow up visit where they too can be assessed for neurodevelopmental delay.

This study may guide therapists working in an NICU or neonatal unit and at follow up clinics, as to how to identify infants who need timeous neurodevelopmental screening or therapeutic intervention. It may also guide doctors when deciding on which infants are most in need of neurodevelopmental assessments, particularly during a busy clinic with many infants presenting for follow up.

5.6 Limitations of the study

This study looked at an age range between three and seven months corrected age, which is young. This fact may have been a limitation as infants have perhaps not reached their true potential developmentally. Also associated

with this limitation is that not all conditions, for example CP, may be diagnosed before seven months and the low rate of CP in this study population (5%) may be inaccurate. Infants were not followed up subsequently at different ages, limiting the Bayley-III results to one assessment only.

Although the Bayley-III neurodevelopmental assessment is normative referenced and valid and reliable in the South African context, another limitation of this study is that there was no control group of infants who were not admitted to the NICU.

5.7 Recommendations for further research

This study demonstrates that neurodevelopmental assessment and screening of high-risk infants is important, in order to start appropriate early intervention when it is needed. However, this study only included infants discharged from an NICU. It is recommended that a larger study be done, including infants not only from NICU but also from high care and the general neonatal ward. It is also recommended that neurodevelopmental assessments be carried out at different ages for a long-term period, which will give a more accurate picture of an infant's neurodevelopment as well as identify significant risk-factors for adverse neurodevelopment. Intervention strategies then need to be implemented timeously where needed, to facilitate normal development and optimal functioning of an infant.

The statistical analysis of this study suggests that in a larger study, inclusion should focus on infants with sepsis, those born via NVD and those who had anaemia. Other complications to pay close attention to are IVH, low birth weight, PDA and RDS. A larger study would also be recommended to assess the effects of NNJ, NEC and twin or triplet pregnancy as these factors showed trends in the current study for being almost significant risk factors for abnormal neurodevelopment.

Chapter 6: **Conclusion**

Literature describes the significant effect that admission to an NICU can have on an infant's neurodevelopment (Leppert & Allen 2012; Pineda et al. 2014). During the most critical stage of an infant's neurodevelopment, they may be exposed to the harsh environment of an NICU and are extremely vulnerable to the adverse effects of neonatal complications and certain life-saving procedures (Pineda et al. 2013; Massaro et al. 2006). These fragile infants are at risk of adverse neurodevelopment, and it is highly recommended that they are assessed with an appropriate neurodevelopmental assessment by a trained professional during their early childhood until school-going age (Leppert & Allen 2012; Hilderman & Harris 2014; Greene et al. 2013). In the instance where neurodevelopment is found to be abnormal, early developmental intervention can commence (Spittle et al. 2012; Vanderveen et al. 2009; Litt & Perrin 2014).

The aim of this study was to conduct neurodevelopmental assessments on infants who graduated from the NICU at CHBAH in Gauteng. Measuring physical growth and documenting birth and clinical data were objectives of this study.

The 40 participants in the study were assessed at a corrected age between three and seven months by a physiotherapist, using the Bayley Scales of Infant and Toddler Development. The neurodevelopmental assessments were conducted at the NNFUC which runs once a week at the hospital. Results were analysed together with the birth history and clinical data of each participant, as well as growth measurements. Early intervention was implemented for participants who showed risk of developmental delay, however all caregivers were educated on how to facilitate normal development, regardless of assessment outcome. Participants were not followed up again.

When analysing the results of this study it is clear that infants who had fewer complications during NICU admission had higher neurodevelopmental scores on the

Bayley-III. Infants who had many (or more than four) complications in NICU were more likely to have lower scores on the Bayley-III assessment. In the same token, infants in this population who had a shorter admission to NICU scored higher than those who had lengthy admissions in NICU. This would suggest that particular attention should be paid to infants with long durations of stay and several comorbidities or complications, after discharge, and it is highly recommended that these infants undergo formal neurodevelopmental assessment.

While it is not possible from the results of this study to determine which factor or complication *independently* poses a risk for abnormal neurodevelopment, they can be highlighted from the data of the lowest scoring participants as well as the statistically significant data. The results of the statistical analysis suggest that particular attention should be paid to infants diagnosed with sepsis, anaemia and those born via NVD when planning follow-up assessment and intervention. As evidenced by the descriptive analysis, infants diagnosed with a genetic condition should be referred to a therapy service when they are deemed medically stable, so as to begin early intervention as soon as possible. Infants with neurological sequelae and those with conditions requiring surgery are also high-priorities for neurodevelopmental screening and early intervention.

However, the mean Bayley-III scores of the population presented in this study (ranging from low average to average) would suggest that all infants who are discharged from an NICU are at risk for a degree of neurodevelopmental delay. Ideally all these infants should be assessed using a formal neurodevelopmental test.

As stated in the beginning of the study, time and resources are limited in the NNFUC setting at CHBAH and at many other state hospitals in South Africa. This research may serve as a guide to therapists, doctors and other health care workers when prioritising infants in need of neurodevelopmental assessment and therapeutic services.

Chapter 7: **References**

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Appendix 1

Information sheet

The neurodevelopmental outcomes of Neonatal Intensive Care Unit survivors attending the Neonatal Follow Up Clinic at a central academic hospital in Gauteng.

Dear Parent

My name is Samantha Rosie, I am a physiotherapist at Chris Hani Baragwanath Academic Hospital. I am currently conducting a study as part of a Master's degree in Physiotherapy being done through the University of the Witwatersrand. The research will serve to help us understand how babies develop if they have spent time in ICU. This information will aid in identifying which babies will need therapy in order to promote normal development.

I am asking permission to use your baby's hospital file to collect information regarding their admission. Weight and height measurements will be taken and then a detailed assessment will be performed to assess their development. This will take approximately 45 minutes. The assessment has 3 stages; motor, language and cognition. You will be able to ask questions at any time.

All the personal information will be kept confidential and no information that could identify your child will be used in the research report. Participation in the study is voluntary. You may withdraw from the study at any stage and there will be no adverse consequences to any person if you refuse to participate or withdraw your participation. There are no risks involved in the study, nor direct benefits.

Thank you for your time.

If there are any questions or if you require more information, please contact the researcher.

Samantha Rosie

Physiotherapy department - Chris Hani Baragwanath Academic Hospital

Contact: 0828272260

0119338309 / 8818

Human Research Ethics Committee (Medical) (HREC) contact: 011-717-2700

Appendix 2

Consent Form

I _____, hereby give consent for my child _____ to be assessed for the study entitled: The neurodevelopmental outcomes of Neonatal Intensive Care Unit survivors attending the Neonatal Follow Up Clinic at a central academic hospital in Gauteng. I give permission to the researcher to access my child's hospital records.

I may change my mind at any time.

I understand that there are no risks involved in this study.

Signed	Witness
_____	_____
Date:	Date:
Place:	Place:

Appendix 3

HISTORY

STUDY CODE:

DOB:	BW: CW:
Gestational age:	Length:
Chronological age:	Head circ.:
Corrected age:	Maternal age:
Gender:	Maternal drugs:
Apgar 1 min.:	Apgar 5 min.:
Mode of delivery:	ICU adm. date:
ICU LOS:	Step down ward:
Time to d/c:	Mode of vent./O_2:
Duration of vent./O_2:	Feeding method:
Resus. Details:	Cranial U/S report:

Circle:

RVD exp.:	Yes / No	NNJ:	Yes / No
PCR pos.:	Yes / No	NEC:	Yes / No
KMC:	Yes / No	Surgery:	Yes / No
PDA:	Yes / No	RDS:	Yes / No
CLD:	Yes / No	MAS:	Yes / No
HMD:	Yes / No	NE:	Yes / No
PVL:	Yes / No	IVH:	Yes / No
CVA:	Yes / No	HIE:	Yes / No
PA:	Yes / No	T/F:	Yes / No
Sepsis:	Yes / No	Seizures:	Yes / No
Multi preg.:	Yes / No	Allied rx:	Yes / No

Other complication: _____
_____
_____

Other abnormality: _____
_____

Appendix 4:

Protocol

The neurodevelopmental outcomes of Neonatal Intensive Care Unit survivors attending the Neonatal Follow Up Clinic at a central academic hospital in Gauteng.

Samantha Rosie BSc Physiotherapy (Wits)

0704379G

Supervisors: Prof. J Potterton

S Pilusa

Contact: samc.rosie@gmail.com

0828272260

Introduction:

Over the past four decades, neonatology has made astounding advances in intensive care which has improved outcomes and survival of premature infants and infants with serious medical and surgical conditions (Browne 2011; Khan-D'Angelo et al. 2012). These infants are termed *high risk*. Most commonly, *high risk* refers to the likelihood of neurodevelopmental disability, which is a group of interrelated, chronic, non-progressive disorders of the central nervous system caused by injury to or malformation of the developing brain (Leppert & Allen 2012).

The long term effects that the neonatal intensive care unit (NICU) environment as well as varying neonatal morbidities have on NICU graduates may be detrimental (Pineda et al. 2014; Leppert & Allen 2012) . NICU graduates may present later in infancy or childhood with different degrees of developmental delay, or other long term complications. Severity and number of complications can be used to identify infants at high risk for disability (Leppert & Allen 2012). Neonates in an ICU environment are among the most fragile patients that physiotherapists will assess and treat, and detrimental effects can occur with routine medical or nursing procedures (Khan-D'Angelo et al. 2012).

Aly et al. (2010) define developmental delay as the inability of a child to acquire developmental milestones at the expected age, 'age-appropriate' functionality, even after allowing for the broad variation of normality. It may be restricted to one domain or be a global developmental delay. Early identification of infants with developmental delay or disabilities will lead to treatment and interventions, which can lessen the impact on the functioning of the child (Aly et al. 2010).

When assessing an infant's development there are many standardised assessment tools available, many of which are not validated for use in under-resourced settings in a developing country. The most widely used standardised and norm-referenced tool is the *Bayley Scales of Infant Development* (Whitehead et al. 2013). It is a set of developmental scales designed to measure developmental functioning. The most

recent version is the *Bayley Scales of Infant and Toddler Development third edition (Bayley III)* (Lennon et al. 2008). It was released in 2006, and has since been shown to be both valid and reliable (Bayley 2006; Whitehead et al. 2013). This edition can be used to assess infants with below normal birth weights and earlier gestational age, as well as significant neonatal risk factors. The *Bayley III* assesses components such as motor, language, and cognitive development (Lennon et al. 2008).

NICU graduates, who are at risk of poor neurodevelopmental outcomes, need to attend comprehensive follow up appointments (Maitre et al. 2013). Many babies who attend such clinics and do not present with obvious neurological deficits or developmental delay, are often not referred to allied services such as physiotherapy. Many of these cases that appeared in infancy to be normal, present at later ages with subtle disorders such as attention deficit and specific learning disorders (Gücüyener et al. 2006). It is therefore important that all NICU graduates attend a follow up clinic and undergo developmental screening as early as possible, where a multidisciplinary approach may be implored to facilitate normal development. Some deficits such as poor vision, hearing deficits, cerebral palsy, and other significant developmental delay appear earlier and appropriate early intervention can commence (Gücüyener et al. 2006).

In 2012, there were 22592 live births at Chris Hani Baragwanath Academic Hospital (CHBAH) (Nakwa 2012). Of these, 699 were admitted over the year to the 12 bed NICU. At this hospital there is a dedicated Neonatal Follow Up Clinic (NNFUC) that runs once a week. NICU graduates return at six weeks post discharge or earlier where necessary. Also included in this clinic are babies who were admitted at the hospital post-natally, but not admitted to NICU. In 2013, a total of 3630 babies attended the NNFUC, giving an average of 303 babies a month.

All allied disciplines provide a service in the NNFUC, including physiotherapy, occupational therapy, speech therapy, audiology and dietary. There is a high load of

patients attending the clinic and unfortunately not all babies receive developmental screening. Developing countries such as South Africa readily adopt the afore-mentioned advances in neonatal care but fail to provide the adequate follow up that is needed for high risk infants. This leads to a significant contrast in the level of care received in NICU and at follow up clinics which are often poorly resourced (Ballot et al. 2012).

Problem statement:

It is important to identify high risk infants who could benefit from developmental screening, as well as early intervention where needed. The NNFUC at CHBAH has inadequate staffing, time, clinical space, equipment, and basic amenities. Therefore a streamlined and comprehensive way of developmental screening would be beneficial in view of these limitations. Assessing the neurodevelopmental outcomes of the NICU graduates and identifying the most high risk infants, would aid this process.

Research question:

What are the neurodevelopmental outcomes of NICU graduates at CHBAH?

Aim:

To assess the neurodevelopmental outcomes of babies discharged from the CHBAH NICU when they attend the NNFUC.

Objectives:

4. To assess neurodevelopmental outcomes at 3 months corrected age or at the corresponding follow up appointment between 3 and 6 months
5. To measure physical growth since NICU discharge at follow up

6. To identify associations between neurodevelopmental outcomes and birth history and clinical data

Method:

1. Study Design

This is a cross-sectional observational study.

2. Study population

Participants will include NICU graduates attending the NNFUC at CHBAH from September 2014 to July 2015, where screening will be performed to identify eligible participants.

3. Inclusion Criteria

Babies who have graduated from the NICU at CHBAH.

4. Exclusion Criteria

Babies diagnosed with Hypoxic Ischaemic Encephalopathy (HIE) II and HIE III are excluded, as they attend a different follow up clinic. Babies who were admitted only to the Neonatal Theatre unit are excluded as they attend a different follow up clinic.

5. Study sample

Statistics have been used to calculate a study sample. In 2012 there were a total of 699 babies admitted to the NICU at CHBAH, giving a mean of 58 babies admitted monthly. Based on a population of 700 babies a year with a confidence interval of 15 and a 95 percent confidence level, a sample of 40 participants is needed for this study.

6. Ethical clearance

Ethical clearance will need to be obtained from the Committee for Research on Human Subjects of the University of the Witwatersrand. Permission will need to be granted by CHBAH to conduct the research on the premises and on patients of this

hospital. Informed written consent will need to be obtained from the caregiver of each participant. This will be translated where necessary. All information and records collected from participants will be used solely for the purpose of the study, and will be kept confidential. Privacy of participants will be respected in a closed room.

7. Measurement tools

Developmental assessment tool: *Bayley Scales of Infant and Toddler Development Third edition*

Weight: The *SECA* infant weighing scale

HLength: The *DEAN* infant measuring board

Head circumference: Standard measuring tape

Clinical data: Data sheet (attached)

8. Procedure

Participants will be screened at the NNFUC once a week. If their corrected age is between 3 and 6 months, and they meet the inclusion criteria, the caregiver will be invited to participate. This is their regular follow up appointment therefore there will be no extra transport cost for caregivers.

Caregivers attending the clinic with the baby will be given an information sheet explaining the research study and assessment. If they agree to their baby participating in the study, they will be given a consent form to sign. The participant and caregiver will be invited into a closed room where privacy can be respected.

All birth history will be collected and recorded on the history form. This clinical data remains with the patient in their hospital file after discharge from hospital. Any subsequent admissions to hospital are also recorded in the hospital file. All this data is with the caregiver at follow up. Weight, length and head circumference will be measured and recorded. A neurodevelopmental assessment will be carried out on

the participant, using the *Bayley III*. The assessment tool will be explained to the caregiver beforehand. Each scale, namely motor, language and cognition, will be administered to participants. In cases where participants are born preterm, the participant's age will be corrected (adjusted) using 40 weeks gestation as the full term reference. Standard scores are derived by referring to the norms table appropriate for this adjusted age (Lennon, et al., 2008). The researcher will do all of the assessments. The researcher is trained in the use of this tool and has performed these assessments in another study. The results will be recorded on the outcomes form.

All participant information will be kept in a filing system and kept confidential.

9. Data Analysis

Descriptive statistics e.g. mean and standard deviations will be used to describe the demographic characteristics of the population. Frequencies will be used to summarise the medical histories of the participants. The scores from the *Bayley III* will be presented as means and standard deviations. A regression analysis and correlations will be used to determine whether there are any relationships between demographic and clinical data and the *Bayley* scores.

Scoring is as follows (Bayley, 2006), and will be presented in a table.

Qualitative descriptions of composite scores from each domain

130 and above	Very Superior
120-129	Superior
110-119	High Average
90-109	Average
80-89	Low average
70-79	Boarderline
69 and below	Extremely low

10. Budget

Photocopying of forms (as attached): (3 x 40) x 25c = R30

Photocopying of assessment forms: (50 x 40) x 25c = R500

Total = R530

11. Timeline

2014

	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sept	Oct	Nov	Dec
Protocol submission												
Protocol assessment												
Present to dept.												
Ethics submission												
Data collection												

2015

	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sept	Oct	Nov	Dec/ Jan 2016
Data collection												
Data analysis												
Write up/submission												

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Page	Examiners' comments	Change made	New page
8	Reference not in reference list (Hoekelman & Simeonsson 1992)	Reference removed, not found	8
14	Does GA or BW have a larger impact on neurodevelopment?	Expanded explanation of importance of birth weight	14
14	Explain CLD and poor nutrition	Explanation added	14/15
21	Explain link between breast feeding and HIV transmission	Explanation and reference added	21
25	Include antenatal information under ethics	Included caregivers' information	25
26	History sheet or data sheet?	Data sheet changed to history sheet	26
26	Not all surgical patients were excluded, yet it is an exclusion criteria	Explanation of inclusion of infants who underwent surgery during NICU admission	26
26	How were infants recruited?	Explanation of recruitment	26/27
27	Explain case of difficult behaviour	Explained procedure with adverse infant behaviour	27
28	Who captured and processed the data?	Included person responsible or data capturing and processing	28
30	Include number of refusals	Added refused consent	30
30	Table 4.1 does not show lowest BW and GA	Corrected explanation of table and results	30
38	Add percentages to pie charts	Labels added to pie charts	38
43	List complication of highest scoring participants	Included complications of these participants	43+49
45	Clarify statement of not comparing studies	Added explanation of broad inclusion criteria and difficult comparisons	46
47	Add reference for statement on Bayley-III in SA	Reference added	47
54	Why are blood transfusion and anaemia not one variable?	Explained that blood transfusion and anaemia were recorded separately in participant files	54
55	Why are HMD and RDS two different variables?	Explanation on data recorded as written in participants' files	55/56
57	Highlight complications posing a risk to neurodevelopment	Complications already discussed	57
42	Change IVH (p=0.58)	Changed to IVH (p=0.058)	42
45	Mention Ballot et al. study only included LBW infants	Added that participants in Ballot et al. study were LBW infants	45
52	Change positive HIV test to HIV infection	HIV test changed to HIV infection	52
55	How many infants had exchange transfusion?	Added that exchange transfusion was not reported as a treatment	55

56	Definition of HIE vs NNE	Explanation of each variable, they are separate. NNE with seizures is not HIE II	56
58	Include Down syndrome participant as a limitation	Included as a limitation	58
63	Fernandez et al. (2012) not included in reference list	Included reference in reference list	63
65	Dates with reference not corresponding	Checked and corrected date on reference	65