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THE EFFECT OF AN IN-PATIENT PHYSIOTHERAPY PROGRAMME IN THE NEONATAL INTENSIVE CARE UNIT ON LONG-TERM DEVELOPMENTAL OUTCOMES OF PRE-TERM INFANTS

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0300487x

A thesis submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in fulfilment of the requirements for the degree PhD.

Johannesburg, 2019

DECLARATION

I, Diana Coetzer, declare that this Thesis is my own, unaided work, except to the extent indicated in the reference citation and acknowledgements. It is being submitted in fulfilment of the requirements of the degree of Doctor of Philosophy at the University of the Witwatersrand. It has not been submitted before for any other degree or examination in any other University.

Diana Coetzer

_____ day of _____ 2019

Dedication

This PhD is dedicated to my family. There are no words for all the support and understanding that you have given to me over the years. Thank you for always pushing me to try harder and do better.

My prayer is that my children will see this and know that they can accomplish anything that they set their mind to!

ABSTRACT

Background:

Infants who are born prematurely have enormous odds to overcome. These challenges range from immediately life-saving to long-term developmental outcomes. Pre-term infants are at risk for delay in all developmental areas due to the timing of the maturation of the various bodily systems and their birth. The delay has been shown to have a direct link with the gestational age of the infant, with an earlier gestational age demonstrating a greater risk for developmental delay. This delay ranges from mild learning disabilities to severe and life-long disabilities. There are various early physiotherapy intervention programmes, but they are costly to implement and not easily available in all countries. Additionally, it is not known which components of these programmes are most effective in improving developmental outcomes.

Aim of the Study:

The aim of this study was to develop and assess the effect of a NICU developmental programme on the developmental outcome of pre-term infants at six, 12 and 18 months.

Methodology:

The programme development consisted of an expert group panel discussion where the proposed programme was discussed and amended accordingly. This early intervention developmental programme consisted of passive movements and joint compressions, massage and nesting with specific positioning done. These various components were discussed with an expert panel on neonates.

The programme was implemented for pre-term infants in one NICU. These infants were the experimental group. A neighbouring hospital NICU was used as the control group. Seventy infants were recruited in each group. These infants were then

assessed by a blinded assessor at six, 12 and 18 months corrected age using the Bayley Scales of Infant and Toddler Development III (BSID III) to determine their developmental status. Caregivers signed informed consent for their infants to participate. Ethical clearance for the study was obtained from the University of the Witwatersrand. Data was analysed using Chi-square tests, means, frequencies and ratios and a linear regression analysis was done.

Results:

The groups were well matched for gestational age. The mean gestational age was 32.80 weeks in the experimental group and 32.50 weeks in the control group (p=0.53). The results of this study showed that the experimental group had an improved developmental status when compared to the control group. This was the result in all developmental areas that the BSID III tests namely, gross and fine motor ($p<0.0001$ at all testing ages), expressive and receptive communication ($p<0.0001$ at 12 and 18 months) and cognitive ($p<0.001$ at six months) developmental areas.

At six months the cognitive scaled scores for the experimental group were 9.70 ± 0.95 and 8.50 ± 0.96 for the control group. The six months expressive language scaled scores were 9.80 ± 1.24 for the experimental group and 10.80 ± 1.24 for the control group. The receptive language scaled scores for the experimental group were 10.80 ± 1.24 and the control group 9.90 ± 1.59. The fine motor six month scaled scores for the experimental group were 10.73 ± 1.80 and 10.10 ±1.93 for the control group. The gross motor six months scaled scores for the experimental group were 8.55 ± 1.76 and 7.80 ± 2.20 for the control.

At 12 months the cognitive scaled scores for the experimental group were 9.90 ± 0.88 and 9.50 ± 1.19 for the control group. The 12 months expressive language scaled scores were 10.20 ± 1.37 for the experimental group and 9.40 ± 0.89 for the control group. The 12 months scaled receptive language scores for the experimental group were 14.20 ± 1.3 and the control 13.80 ± 0.93. The fine motor, 12 month scaled scores

for the experimental group were 10.28 ± 0.98 and 9.00 ± 1.26 for the control group. The gross motor 12 months scaled scores for the experimental group were 10.60 ± 1.37 and 8.50 ± 1.86 for the control.

At 18 months the cognitive scaled scores for the experimental group were 10.20 ± 0.99 and 9.30 ± 1.83 for the control group. The 18 months expressive language composite scores were 98.69 ± 5.14 for the experimental group and 95.20 ± 5.10 for the control group. The 18 months receptive language scores for the experimental group were 10.30 ± 0.88 and the control group were 9.50 ± 1.23. The fine motor 18 month composite scores for the experimental group were 10.44 ± 1.18 and 9.00 ± 0.97 for the control group.

The linear regression analysis showed that in all three developmental areas the intervention was predictive of the developmental outcome. Factors that were found to be predictive of poorer developmental outcome, at 18 months of age in the control group for motor development, were that of NEC (t=0.01) and gestation (t=0.02). In the language section, the regression showed surfactant (t=0.04) to be the significant factor. In the cognitive section surfactant (t=0.01) and gestational age (t=0.04) to be the factors predictive of poorer developmental outcome.

Discussion and Conclusion:

This study shows that a developmental intervention consisting of passive movements, joint compression, massage and nesting provided while the infant is in NICU is an effective programme to decrease the risk of developmental delay in this vulnerable population. The results of this study are important as the programme can be implemented into various hospitals with NICUs to aid in the improvement of the morbidity of this population group and the results show that physiotherapy can reduce the burden of disease in this population group by allowing for stimulation during the important brain plasticity phase and decreasing the risk of possible developmental delay. This can be easily implemented into any NICU that has a physiotherapist.

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- The caregivers and children who participated in the study

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LIST OF ABBREVIATIONS

ADHD	Attention deficit hyperactivity disorder
AGA	Appropriate-for-gestational-age
AIMS	Alberta Infant Motor scale
ANOVA	Analysis of variance
BiPAP	Biphasic positive airway pressure
BMI	Body Mass Index
BSID II	Bayley Scales of Infant Development 2nd edition
BSID III	Bayley Scales of Infant and Toddler Development 3rd edition
CNS	Central Nervous System
CP	Cerebral palsy
CPAP	Continuous positive airway pressure
EEG	Electroencephalography
EI	Early intervention
ELBW	Extremely low birth weight
EMG	Electromyography
GABA	Gamma-aminobutyric acid
GAPPS	Global Alliance to Prevent Prematurity and Stillbirth
GM	General movements
HIV	Human immunodeficiency virus
HRQoL	Health-related quality of life
ITB	Ilio-tibial band
IQ	Intelligence Quotient
IUGR	Intrauterine growth restriction
IVH	Intraventricular haemorrhage
KMC	Kangaroo mother care
MRI	Magnetic resonance imaging
NDT	Neurodevelopmental Therapy
NGST	Neuronal Group Selection Theory
NICU	Neonatal Intensive Care Unit
NIDCAP	Newborn Individualised Developmental Care and Assessment Program
NMDA	N-methyl-D aspartate

OT	Occupational Therapy
PMA	Postmenstrual age
PNS	Peripheral Nervous System
PROM	Premature rupture of membranes
PVHI	Periventricular haemorrhagic infarction
PVL	Periventricular leukomalacia
RDS	Respiratory distress syndrome
REM	Rapid eye movement
ROP	Retinopathy of prematurity
TIMP	Test of Infant Motor Performance
SD	Standard deviation
SGA	Small for gestational age
SIMV	Synchronised intermittent mandatory ventilation
TCPL	Time-cycled pressure-limited
VLBW	Very low birth weight
WHO	World Health Organisation

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Chapter 1: INTRODUCTION

1.1 Background

Infants who are born prematurely have enormous odds to overcome when compared to the average full-term infant. These challenges range from immediate life-saving challenges to long-term developmental outcomes (Blencowe et al., 2013a; Blencowe et al., 2013b; Moster et al., 2008).

Prematurity is defined as an infant being born prior to 37 weeks of gestational age (Purisch and Gyamfi-Bannerman, 2017; Blencowe et al., 2013a; Blencowe et al., 2013b). Research has shown that children who are born prematurely may show signs of developmental delay later in life (Johnson, 2007). It has been shown that developmental outcome is related to gestational age. For example, infants born within the 22 – 26 week gestation period had a higher rate of neonatal morbidity and neurodevelopmental delay at 18 months than the 27 – 37 week gestational age infants as well as those infants born small for gestational age (SGA) (Slykerman et al., 2007). Children born at less than 26 weeks gestational age have been shown to be at risk of Grade III/IV intraventricular haemorrhage and periventricular leukomalacia which may result in cerebral palsy (Tsimis et al., 2015).

In developing countries such as South Africa, prematurity is estimated to be at 12.4% (Chawanpaiboon et al., 2019). The 2012 World Health Organisation report of prematurity presented an 8% pre-term birth rate (March of Dimes et al., 2012). Fifty five percent of pre-term infants are male (Blencowe et al., 2013a; Blencowe et al., 2013b). Hediger et al., (2002) also found that pre-term males had a higher incidence of delayed motor and social development on assessment when compared to pre-term females (Hediger et al., 2002). There is no specific cause of prematurity. Risk factors include multiple pregnancies; genetic predisposition; infections and chronic conditions such as hypertension (Blencowe et al., 2013a). It has been reported that infection is the greatest cause of pre-term labour (Muglia and Katz, 2010). In South Africa these

infections were shown to be mainly Human Immunodeficiency virus (HIV) and malaria (Steer, 2005). These are important concerns in the South African context as HIV affects 23.8% of South African women (UNAIDS, 2017). A study in Bloemfontein hospitals reported however, that teenage mothers with various pre-existing conditions, such as HIV and hypertension, had premature rupture of membrane as the main risk factors for pre-term birth (Brits et al., 2015). Many women in South Africa are forced to take employment that requires them to put their own health and that of their unborn child at risk to earn a living in order to support their family. These include various occupations involving manual labour, which may predispose them to additional risk for pre-term labour (Michalowicz and Durand, 2007). Social factors such as smoking, drug use and occupational hazards have been shown to cause pre-term birth (Weck et al., 2008). Pre-eclampsia and maternal hypertension are another two of the major pathologies causing pre-term labour (Steer, 2005).

Prematurity has been shown to have effects on many facets of development (Blencowe et al., 2013b). The impairments range from mild learning disabilities to severe life-long disabilities. The research has shown that this broad range of disability can affect early as well as late pre-term infants (Coletti et al., 2015).

Prematurity has been linked to cognitive developmental delay (Poulsen et al., 2013). A study compared groups of infants in the ranges of: 23 – 31 weeks gestation; 32 – 33 weeks gestation; 34 – 36 weeks gestation; 37 – 38 weeks gestation; and full term of 39 – 41 weeks gestation. The study only assessed cognitive function. This study showed that half of the pre-term infants, of a sample size of 283 that survived, suffered from neurological delay. The main finding was that cognitive ability was related to gestational age across all testing ages (Poulsen et al., 2013). Further studies have shown that cognitive delay is more common than motor delay in infants born pre-term, and difficulties with reading and spelling increased with a decrease in gestational age (Allen, 2008). This study also showed that cognitive impairments were not only due to early gestational age and low birth weight, but also due to the various types of brain injuries that may be associated with prematurity such as intraventricular haemorrhage and periventricular leukomalacia (Allen, 2008).

Delayed language development has been linked to prematurity (Stolt et al., 2014). Poorer vocabularies are linked with varying degrees of brain injuries that were mentioned above. It has been established that pre-term children used less complex expressive language and demonstrated slower receptive language skills when compared with term-born infants (Schirmer et al., 2006). A study conducted by Ortiz-Mantilla (2008), showed that the language delay in infants with low birth weight could be linked to a global cognitive delay (Ortiz-Mantilla et al., 2008). Research conducted on the language organisation system in pre-term infants showed that there is longer atypical language organisation when compared with full term infants. This may be an explanation for the language delay in pre-term infants and is again linked to gestational age (Mürner-Lavanchy et al., 2014).

Motor development consists of both fine and gross motor development. Studies have shown that prematurity has a role to play in delayed motor development. Bucher et al, 2002, showed that 18% of their sample were not able to walk at 18 months corrected age. This was compared with the control group who attained walking at 13.5 months (Bucher et al., 2002). Findings have also demonstrated that gross motor scores on various developmental tests are below average for pre-term children at various ages (Goyen and Lui, 2002). This study also showed that over 50% of the pre-term sample suffered from fine motor deficits at eighteen months corrected age. Motor developmental impairments have also been shown to occur in low-birth weight children that were born prematurely (Oberg et al., 2012).

Developmental care programmes have been documented to improve short- and long-term neurological outcomes (Peters et al., 2009). Many of the studies only assess infants born prior to 32 weeks and infants with very low birth weight (Peters et al., 2009). This leaves a large proportion of the pre-term population at-risk for developmental delay (Woythaler et al., 2015).

Developmental assessments are used to allow clinicians and researchers insight into the level of functioning of a specific group. This allows comparison against a normal population group which in turn allows for various treatment, planning and advocacy improvements for the specific population group that is being assessed (Milne et al., 2012; Spittle et al., 2008). There are several different tools available to assess developmental functioning which vary in administration length, infant handling, reliability and predictive validity (Spittle AJ, 2015). The Bayley Scales of Infant and Toddler Development is considered the gold standard in developmental assessment. It has been used in research on child development in many countries around the world, including in South Africa (Duncan et al., 2015; Luttikhuizen dos Santos et al., 2013; Currie et al., 2012). A study conducted on the South African population in 2016, reported that the Bayley Scales of Infant and Toddler Development demonstrated the best predictive value for at-risk infants (Richter et al., 2016).

Intervention in the Neonatal Intensive Care Unit (NICU) is infant-driven and should be evidenced-based. It allows for family-centred care (Byrne E, 2013). Intervention programs are available worldwide but do not seem to be currently implemented in the majority of South African NICUs. These early intervention programs all vary in design and cost of training (Nordhov et al., 2010). The Newborn Individualised Developmental Care and Assessment Program (NIDCAP) is one of these developmental care programs. The NIDCAP course consists of a training program which requires an instructor to come to the hospital. The training involves observations, lectures and patient reports (Als, 1986). This is time-consuming training and due to the cost involved not many state or private hospitals in developing countries, such as South Africa, will do the training. The NICU also then needs to convert to a NIDCAP nursery which has further cost implications. A systematic review of 11 randomised controlled trials involving 627 neonates, could not find any significant benefits to the NIDCAP programme in its current form (Ohlsson and Jacobs, 2013). Therefore, an expensive course is not required to practice developmental care in the NICUs.

A different developmentally supportive programme is required due to the fact that NIDCAP is an extremely expensive and time-consuming exercise. The NIDCAP

programme is not very well supported by the evidence. Even though certain aspects of individualised, developmental programmes are not well supported by evidence the concept of developmental care is (Maguire et al., 2009b).

1.2 Problem Statement

The majority of Neonatal Intensive Care Unit developmental programmes require expensive training and are not readily implemented in developing countries. Many pre-term infants in South Africa both in the private and public sector do not receive any developmental intervention or follow-up at all, despite being known to be at risk for developmental problems. This is often due to a lack of knowledge from the parents and the incorrect advice being given. A need exists for cost-effective and sustainable developmental intervention strategies. A standardised approach to developmental care in South Africa is required.

1.3 Research Question

Does a NICU Developmental Programme have an impact on the developmental outcomes of South African pre-term infants?

1.4 Aim

The aim of this study was to develop and assess the effect of a NICU Developmental Programme on the developmental outcome of premature infants.

1.5 Objectives

- To develop a NICU developmental programme.
- To establish the developmental status of infants aged 18 months corrected age who received the programme whilst in NICU.
- To establish the developmental status of infants aged 18 months corrected age who did not receive the programme whilst in NICU.

- To compare the two groups in terms of motor, cognitive and language development at corrected gestational age and then at six monthly intervals until they are 18 months old (corrected age).
- To determine whether clinical and demographic data are associated with developmental outcome.

1.6 Contribution to field:

There is currently no generally accepted approach to the developmental care of premature infants in South Africa. This study will provide insight into the developmental challenges experienced by premature infants and may provide some preliminary treatment ideas.

Chapter 2: LITERATURE REVIEW

Knowledge of the central nervous system and the development thereof is vital in allowing us to gain an understanding into how the various areas of the body can be affected by prematurity. This literature review will discuss the normal development of the domains of cognitive, motor and language development. This will then be considered in regard to effects of prematurity.

The literature was obtained through PubMed, Medline and PEDro searches. Keywords used in the searches included: prematurity; normal development; abnormal development; massage; passive movements; range of motion; sensory development; positioning; joint compression; positioning; kangaroo mother care; occupational therapy; therapy in South Africa; therapy in Neonatal intensive care units; cognitive development; language development and early intervention in the neonatal intensive care units. Search parameters included English articles and the date range for the majority of the literature was from was 2003 to 2018, apart from seminal older texts. Research conducted in South Africa was sought to include in this study. There is little research that has been conducted on this topic on the South African population. All study designs were considered for the literature review to ensure that various views were seen for literature synthesis.

2.3 The Definition of Prematurity

Prematurity is defined as an infant that is born at less than 37 completed weeks of gestation (Purisch and Gyamfi-Bannerman, 2017; Swamy et al., 2008) or 259 days of gestation (Beck et al., 2010). Pre-term infants are divided into categories based on gestational age. These include extremely pre-term infants born less than 28 weeks gestation, very pre-term which is infants between 28 and 32 weeks gestation and late pre-term infants born between 32 and 36 weeks gestation (Cheong and Doyle, 2012). Pre-term infants can be divided into categories based on birth weight. These include extremely low birth weight (ELBW) which are infants born weighing less than 1000g (Buddhavarapu et al., 2015). Very low birth weight (VLBW) are infants born weighing

between 1001g and 1500g and low birth weight (LBW) are infants born between 1501g and 2400g (Harrison and Goodman, 2015).

2.1.1 Low Birthweight and Small for Gestational Age

Low birth weight is a common complication of prematurity and has the potential for adverse side-effects. Low birth weight and small for gestational age (SGA) pre-term infants are recorded to make up 15 to 30 percent of pre-term births (Bickle Graz et al., 2015). In South Africa, a follow up study was conducted on 106 VLBW infants and 3.7% of those infants were diagnosed with cerebral palsy (CP) by 18 months of age (Ballot et al., 2012). It has been reported that ten percent of VLBW infants will develop cerebral palsy and cognitive deficits. The most common lesion causing cerebral palsy is periventricular white matter injury (Tsimis et al., 2015). In the VLBW population group those weighing less than 1000g have the highest rates of morbidity and mortality (Mercier et al., 2010).

Small for gestational age is defined as birthweight and, or, length that is a minimum of two standard deviation scores below the mean for gestational age (Castanys-Muñoz et al., 2017). SGA infants have been shown to be smaller for various reasons. These include intrauterine growth restriction (IUGR) due to placental, foetal or environmental factors. These infants have been shown to be at risk for increased neonatal morbidity and mortality especially in the motor developmental area. Children who are born SGA have been shown to have poorer neurodevelopment than children who are born appropriate-for-gestational-age (AGA) (Li et al., 2016). These neurodevelopmental disadvantages have been attributed to structural and functional impairment in the infant's brain development (Li et al., 2016). Possible alterations in white matter development, when combined with cortical grey matter alterations, can cause problems with motor, cognitive and general functioning of the CNS of the SGA population (de Kieviet et al., 2012). Small for gestational age infants have also been shown to be at greater risk for abnormal test scores on attention control at school-going age when compared to AGA peers (Tanis et al., 2015). Various imaging studies conducted on IUGR infants, have shown differences in brain structure and decreased brain volumes when compared to their appropriate birthweight controls. The studies showed reduced grey matter in the temporal, parietal and frontal regions. A decrease

is also found in the white matter of the cerebellum and hippocampus (Castanys-Muñoz et al., 2017; Saunavaara et al., 2017; Bickle Graz et al., 2015; Padilla et al., 2011; Evensen et al., 2009).

Mothers who received poor prenatal care have also been shown to have a greater chance of delivering an infant with a low birth weight (Zeka et al., 2008). The risks of both prematurity and low birth weight were increased with a decrease in the number of ante-natal visits (Raatikainen et al., 2007; Ngoc et al., 2006). Mothers who smoked while pregnant showed a 27% increased risk of pre-term birth with a SGA infant. Included in this risk were that of daily and nondaily smokers (Tong et al., 2017).

2.2 The Global and National Prevalence of Pre-term Birth

In the USA the pre-term delivery rate has been reported at between 12 - 13% (Goldenberg et al., 2008). The global figure for premature birth has been reported at 15 million births per year (Purisch and Gyamfi-Bannerman, 2017). In Europe it is reported to be at 5 - 9% (Goldenberg et al., 2008). High income countries a 9% pre-term rate compared to a 12% rate in lower income countries (World Health Organization, 2017; March of Dimes et al., 2012). In developing countries such as South Africa, prematurity is estimated to be at 12.4% (Chawanpaiboon et al., 2019). The 2012 World Health Organisation report of prematurity from 2012 presented an 8% pre-term birth rate (March of Dimes et al., 2012).

It has been reported that there are more males born prematurely than females (Peacock et al., 2012). A study conducted in 2008 reported that the percentage of males born pre-term was 5.6% as opposed to 4.7% of females (Swamy et al., 2008). The reason for this remains unclear. The first suggested reason for the higher male pre-term birth ratio is that induction of labour may be promoted by interleukin-1 which is found in the amniotic fluid of pre-term males (Shiozaki et al., 2011; Ingemarsson, 2003; Zeitlin J et al., 2002). Further reasons have been attributed to heavier body weight which increases the pre-term birth risk. Male foetuses have been said to have an increased risk of a complications associated with pre-term birth such as pregnancy-induced hypertension (Zeitlin J et al., 2002). It was reported that the ratio of males to

females who are born due to pregnancy-induced hypertension is 1.72 (Shiozaki et al., 2011).

2.3 Risk Factors for Pre-term Birth

Two thirds of pre-term births are idiopathic, one third have been related to premature rupture of membranes (PROM) and from medically indicated deliveries (Purisch and Gyamfi-Bannerman, 2017). The Global Alliance to Prevent Prematurity and Stillbirth (GAPPS) group published a system to classify the causes of prematurity in 2012. This classification system consists of five components: (i) significant maternal conditions, (ii) significant foetal conditions, (iii) placental pathologic conditions, (iv) signs of the initiation of parturition (e.g. cervical shortening, rupture of membranes, bleeding, contractions), and (v) pathway to delivery (e.g. caregiver-initiated or spontaneous labour). The most frequent were not associated with any condition but rather spontaneous PROM (30%), while 22% were found to have a medical cause (Frey and Klebanoff, 2016; Barros et al., 2015). Evidence shows that up to 25% of pre-term births are due to infection (Hutcheon et al., 2011; Muglia and Katz, 2010).

In developing countries, the primary infection that causes prematurity has been shown to be the Human Immunodeficiency virus (HIV) (Steer, 2005). This is a pertinent issue in South Africa, as it was estimated that in 2011 58% of all HIV positive people in the sub-Saharan African region are women (UNAIDS 2012). Another infection that is an issue in South Africa is malaria. Malaria may affect foetal growth through maternal anaemia and placental infection (Simmons et al., 2010).

Premature rupture of membranes is described as a spontaneous rupture of the membranes prior to the onset of labour (Caughey et al., 2008). Risk factors for PROM are infections, tobacco exposure and smoking, short inter-pregnancy intervals and multiple pregnancies (Monangi et al., 2015; Beck et al., 2010; Caughey et al., 2008; Goldenberg et al., 2008). The membranes act as a protective barrier and once these have ruptured there is an increased risk of infection and this has in turn been shown to have an increased risk of neurodevelopmental delay (Caughey et al., 2008).

Another reason for the increase in pre-term births is the increasing number of multiples that are being born due to assistive reproductive technologies (Mesa and Peral, 2011; Goldenberg et al., 2008). A reason for this has also been attributed to the delay in age of childbearing (Mesa and Peral, 2011). Children born from multiple pregnancies present with a greater risk of pre-term delivery. Research has shown that on average 53% of twin pregnancies and 92% of triplet pregnancies present with low birthweight and prematurity occurs in 47% of twin pregnancies and in 91.6% of triplet pregnancies (dos Santos Motta et al., 2011). The occurrence of maternal complications such as pre-eclampsia and pre-term rupture of membranes (PROM) increases with the number of infants carried (Mesa and Peral, 2011).

Other risk factors for pre-term birth are that of work-related physical and psychosocial stress (Wadhwa et al., 2011; Goldenberg et al., 2008; Culhane et al., 2002). Reviews conducted over the last two decades have shown that the women who suffer from stress during pregnancy are at a 25% to 60% greater risk of pre-term birth. These results were across various other parameters of race and socioeconomic backgrounds (Wadhwa et al., 2011). It has been found that stress is associated with poorer maternal nutrition which can cause growth problems in the foetus leading to pre-term birth (Wadhwa et al., 2011). The second aspect is that pregnant mothers who are under stress are at greater risk for infection as high stress levels have been shown to cause a decrease in lymphocyte activity (Wadhwa et al., 2011; Culhane et al., 2002).

Chorioamniotis has been shown to be a major cause for unexplained pre-term birth. Chorioamniotis is an intrauterine inflammation of the chorion and placenta. This condition is caused by bacterial infection (Galinsky et al., 2013; Vrachnis et al., 2010). The inflammatory markers in the amniotic fluid increase, including C-reactive protein and monocyte chemotactic protein-1, both of which increase the risk of chorioamniotis occurring (Vrachnis et al., 2010). The incidence of chorioamniotis is inversely related to the gestational age. It has been shown to be the cause of 16% of pre-term births at 34 weeks gestational age (Galinsky et al., 2013).

There are many risk factors for pre-term birth with varying degree of risk. Research has been conducted into the risk of pre-term birth in the HIV population in South Africa.

This research showed risk factors for premature birth in this population group included teenage mothers, pre-existing medical conditions in the mother and PROM. Further research needs to be conducted into the remaining population (Brits et al., 2015).

2.5 Complications of Prematurity Impacting Development

The shorter the length of gestation is, the greater the risk of postnatal complications. The severity of complications increases with decreasing gestational age (Blencowe et al., 2013b; Katz et al., 2013; Allen, 2008).

2.5.1 Periventricular Leukomalacia

Periventricular leukomalacia (PVL) is a serious complication of prematurity. PVL is defined morphologically by two histopathologic components- (1) a focal, necrotic component in the periventricular region of the cerebral white matter; and (2) a diffuse component characterised by reactive gliosis in the surrounding white matter (Hinojosa-Rodríguez et al., 2017; Resch et al., 2012; Kinney, 2006). During cerebral vascular bed development, the development of the vascular watershed occurs. This takes place on the lateral cerebral ventricles, as well as the white matter surrounding the foramen of Monroe (Berger and Söder, 2015). After the 32nd week PMA the vascularization of these sites increases and for this reason the risk of PVL decreases (Berger and Söder, 2015). It has been found that PVL is caused by a sequence of events. This brain injury has been shown to be caused by inducing a foetal inflammatory response syndrome which activates a cascade of cytokines, which are able to damage the oligodendrocytes in the initial stages of development and by doing this disrupts the myelination process which affects the motor skills development of the infant. The release of endotoxins has been shown to lead to a disruption of the regulation of the foetal cardiovascular system, resulting in a decrease in cerebral blood circulation and therefore ischaemic lesions in the white brain matter. These can cause pre-term labour. The greatest vulnerability is between 24 and 34 weeks PMA (Zaghloul et al., 2017; Laptook, 2016; Berger and Söder, 2015; Kinney, 2006). This complication most commonly leads to damage of the lateral cerebral ventricles and the white matter around the foramen of Monroe (Berger and Söder, 2015).

Periventricular leukomalacia is said to be the most common cause of cerebral palsy in pre-term infants (Tsimis et al., 2015; Hirvonen et al., 2014; Imamura et al., 2013). Causes of PVL include infection, cerebral ischemia and ventilation mode (Berger and Söder, 2015; Peng et al., 2014; Resch et al., 2012; Wheeler et al., 2011). A systematic review conducted on 18 studies showed that infants ventilated using volume-targeted ventilation modes had improved outcomes when compared to infants using pressure-limited ventilation with fewer cases of PVL (Peng et al., 2014; Wheeler et al., 2011). Bacteria and sepsis were shown to be present in 50% of PVL cases in a single-centre retrospective control case study in Austria. The reaction was postulated to be due to the foetal inflammatory response syndrome. When microorganisms or antigens gain access to the foetus, they cause a production of cytokines and a systemic response-the foetal inflammatory response syndrome, which can lead to damage of the infant's brain and other organs (Resch et al., 2012).

2.5.2 Intraventricular Haemorrhage

Intraventricular haemorrhage (IVH) is a major complication of prematurity (Ballabh, 2010). The haemorrhage commonly begins in the germinal matrix. This is a highly vascularized collection of neuronal-glial precursor cells in the developing brain (Roberts et al., 2018; Bolisetty et al., 2014; Merhar et al., 2012; Ballabh, 2010). This complication usually occurs in pre-term infants with a gestational age of 32 weeks or less. The incidence rate is inversely related to the gestational age (McCrea and Ment, 2008). Intraventricular haemorrhage is known to be caused by an alteration in cerebral blood flow to the immature germinal matrix blood vessels. During the risk period this area of the brain is richly supplied with blood vessels but lacks the components of an effective blood-brain-barrier, basement membrane deposition, tight junctions and glial endfoot structures. The brain responds to the various stressors being placed on the system such as hypotension and hypoxemia by increasing the cerebral blood flow and this can lead to a haemorrhage in the germinal matrix which may rupture into the ventricular system of the brain (McCrea and Ment, 2008). For these reasons, disturbances in cerebral blood flow and the fragility of the germinal matrix vasculature primarily contribute the development of IVH. Vasculature density increases with gestational age in the regions of the germinal matrix, white matter and cerebral cortex. The vast vascularity is thought to be due to the high metabolic demand of this

developing brain. The high vascularity increases the risk of a haemorrhage in this area (Ballabh, 2010). The germinal matrix that surrounds the foetal ventricular system gradually moves to its final position between 24 and 28 weeks gestation to the level of the caudate nucleus. This shows that even a small haemorrhage can have an impact on the future functioning of this area of the brain which has a role in memory and language (Bolisetty et al., 2014).

A grading system was developed by Papile et al (1978) and is still used today. Grade I refers to germinal matrix haemorrhage, Grade II to intraventricular haemorrhage without ventricular dilation, Grade III to intraventricular haemorrhage with acute ventricular dilation and Grade IV to a venous infarction known as periventricular haemorrhagic infarction (Bolisetty et al., 2014; Ballabh, 2010; McCrea and Ment, 2008).

There have been numerous studies investigating the causes of IVH. This complication has been linked to low gestational age, maternal infection, absence of antenatal steroid use, sepsis, respiratory distress syndrome and SGA status (Bolisetty et al., 2014; Ballabh, 2010; McCrea and Ment, 2008). Infants who suffer from a Gr I and II IVH have been shown to be at risk for developmental disabilities. While those with Gr III and IV are at high risk for CP with 45% to 86% having been reported to suffer from major cognitive and motor disabilities (Bolisetty et al., 2014; McCrea and Ment, 2008).

2.5.3 Periventricular Haemorrhagic Infarction

Periventricular haemorrhagic infarction (PVHI) is defined as a grade four germinal matrix haemorrhage (Bassan et al., 2007). This complication has been found that between 3% and 11% of premature infants born below 32 weeks' gestation develop PVHI. This complication usually develops from 24 to 96 hours after birth and has been linked to infants who also suffer with cardiorespiratory instability (Soltirovska Salamon et al., 2014; Harteman et al., 2012). Blood vessels in this area burst easily with fluctuations of the cerebral blood flow leading to rupture of these vessels and inducing PVHI (Berger and Söder, 2015). It is thought to be caused by pressure of the germinal matrix haemorrhage on the periventricular terminal vein that drains the cerebral hemisphere. This leads to venous congestion in the periventricular white matter which

causes ischemia and haemorrhage (Roze et al., 2008). There is thought to be an impairment to the medullary vein's drainage in the periventricular white matter and which may be associated with the PVHI and ischaemia of this white matter (Soltirovska Salamon et al., 2014; Harteman et al., 2012). These haemorrhages can be exacerbated by an alteration in the thrombocyte aggregation and coagulation system, leading to germinal matrix destruction, PVHI of the white matter and hydrocephalus (Berger and Söder, 2015). Mortality in PVHI ranges from 38% to 60%. Survivors are at an increased risk of cerebral palsy and neurological problems after 12 months of age (Roze et al., 2008).

There are several other factors that have been linked to PVHI. These include low APGAR scores, need for respiratory resuscitation, pneumothorax and pulmonary haemorrhage (Soltirovska Salamon et al., 2014; Harteman et al., 2012; Roze et al., 2008). This lesion type is associated with both motor and cognitive neurological fallouts (Guo et al., 2017). Bilateral PVHI was shown to have a five-fold increase risk for developing CP (Maitre et al., 2009).

2.5.4 Retinopathy of Prematurity

Another common complication of prematurity is retinopathy of prematurity (ROP). Retinopathy of prematurity is defined as a disorder of retinal vaso-proliferation that occurs mainly in extremely pre-term infants born at less than 28 weeks gestation (Glass et al., 2017; Allred EN, 2014; Hellström et al., 2013). The structural characteristics of ROP are an initial interruption in the retinal vascularisation (Dammann et al., 2009). In a population review study conducted between 1993 and 2012 it was documented that 60% of the infants overall developed ROP. The study population included infants with gestational ages between 22 and 29 weeks and birth weights of between 401g and 1500g. It also showed that there was an inverse relationship between diagnosis of ROP and gestational age (Stoll et al., 2015).

Risk factors for the development of ROP include: excessive oxygen exposure, oxygen-related disturbance of angiogenic growth factor availability, oxygen radicals, and candida sepsis (Dammann et al., 2009). Sepsis showed a strong association with ROP and this was thought to be due to the fact that there is a reduced capacity for these

young infants to mount an inflammatory response. Infection and sepsis have been found to be associated with vision impairments. It is thought that this is due to the ROP being caused by the inflammatory response and not as a result of the infection itself (Chen et al., 2011). With regards to genetic factors it has been shown that ROP is more prevalent in Caucasian infants as well as being more common in males than females (Cavallaro et al., 2014). It has also recently been discovered that there is a higher risk of ROP with certain gene mutations involved with receptor signalling pathways (Cavallaro et al., 2014).

Birthweight and gestational age are also risk factors for ROP. Both these factors are related to the immaturity of the retinal neural structures and vasculature related to the specific gestational age at birth (Hellström et al., 2013). A previous study also found a relationship between respiratory distress syndrome (RDS) and ROP (Akkoyun et al., 2006). Oxygen exposure during phase one of ROP suppresses the vascular endothelial growth factor expression. This results in an interruption to the normal growth of the vessels and also causes regression of the existing vessels (Chen et al., 2011).

Studies have shown that pre-term infants suffering from ROP have an associated lower cognitive and motor score and this was independent of any other white matter injury (Glass et al., 2017). Severe ROP is linked to a maturational delay in the external capsule and posterior white matter. This is where the primary visual and motor pathways which explains the link between poorer cognitive and motor development with ROP (Glass et al., 2017). It has been postulated that, as the retina is a component of the central nervous system, by reducing the risk factors that affect postnatal retinal development this may have a positive effect on brain development and therefore aid in decreasing the associated developmental disabilities that are associated with ROP (Hellström et al., 2013).

2.5.5 Sepsis and Infection

Sepsis has been described as a systemic infection resulting from bacterial invasion and multiplication in the blood stream. It can lead to high risk of neonatal mortality and morbidity (Ferreira et al., 2014). The proposed mechanism behind the brain injury

associated with sepsis has been linked to pre-oligodendrocytes mediated by free radicals, reactive oxygen and inflammatory cytokines (Shah et al., 2008). The clinical signs of this infection are increased temperature, instability, irritability, feeding difficulties, prolonged capillary refill, apnoea and tachycardia (Schlapbach et al., 2011). Studies researching the cellular mechanisms that cause white matter injury in pre-term infants showed that infections are important mediators of the inflammatory-mediated white matter injury which can cause developmental disabilities (Shah et al., 2008). Pre-term infants who have a LBW have been shown to have a 2.5 times higher risk of developing sepsis and have altered neuromotor development at age 12-months (Ferreira et al., 2014; Schlapbach et al., 2011; Shah et al., 2008).

2.5.6 Respiratory Distress Syndrome

Respiratory distress syndrome (RDS) is caused by a lack of pulmonary surfactant. Surfactant is a phospholipid, which stabilises surface tension in the alveolus, and prevents alveolar collapse on expiration. Small quantities are produced at weeks 23-24 weeks of gestation and the amount gradually increases until a surge at week 30. The birthing process and the onset of respiration stimulate surfactant production (Hillman et al., 2012). The pathophysiology of RDS is as follows: the immature type II alveolar cells produce less surfactant, causing an increase in compliance. The resultant atelectasis causes pulmonary vascular constriction, hypoperfusion and lung tissue ischemia. Hyaline membranes form through the combination of sloughed epithelium, protein and oedema (Hermansen and Mahajan, 2015). When an infant is born prematurely, their lungs do not produce enough surfactant and the alveoli collapse, preventing the infant from breathing properly. Babies born full term rarely develop RDS. Most cases are seen in pre-term babies under 28 weeks gestation (Pryor and Prasad, 2003). Symptoms of RDS include: apnoea, cyanosis, grunting, inspiratory stridor, nasal flaring, poor feeding and tachypnoea. RDS occurs in approximately seven percent of p pre-term infants. It is more prominent in male infants (Hermansen and Mahajan, 2015). Data available has shown that pre-term infants who suffered from RDS are at future risk for decreased lung function in life. A poorer developmental outcome has been linked to this and is thought to be due to increased frequency of hospital admissions (Kotecha et al., 2012).

There are unfortunately many possible complications that can affect this population group. Numerous studies have been conducted on these complications and the risks documented. The main group studied for these complications is that of the extremely pre-term group. This is understandable due to the complication risk increasing with decreasing gestational age (Manuck et al., 2016).

2.5 Normal Development

2.5.1 Development of the Central Nervous System

The central nervous system begins developing in the fifth week post menstrual age (PMA) with the formation of the neural tube. This development continues for two decades before the central nervous system obtains its adult formation. Neural proliferation has been shown to have its peak development between weeks five and 25 PMA but continues into adulthood. Neural proliferation is the process where neural tissue differentiates forming the major sub-divisions being: forebrain, midbrain and spinal cord. This continues until the child is five years of age. Axonic and dendritic sprouting peaks between 25 weeks PMA and one year of age. This sprouting only occurs during this part of the development as the central nervous system cells need to have reached their final position prior to this sprouting occurring (Hadders-Algra, 2018; de Graaf-Peters and Hadders-Algra, 2006).

The corticospinal tracts have been shown to be the last of the major tracts to enter the spinal cord. Damage to the thalamus has been shown to be associated with damage to the internal capsule, which houses the ascending and descending tracts. Damage to these structures can give rise to motor deficits (Kugelman and Colin, 2013; Ball et al., 2012). Dendritic formation begins early in foetal life but is slow in the first and second trimester. It accelerates during the third trimester and remains very active until one year of age. It then slows down again until five years of age. The length of both axons and dendrites increases five to ten times in the first six months of post-natal life (Girard et al., 2012; de Graaf-Peters and Hadders-Algra, 2006). Between the 33rd and 35th gestational weeks there is dendritic formation in the cortical plate (Hadders-Algra, 2018). This explains why infants born at this crucial time are also at risk for developmental issues due to an interruption in the brain development (Clouchoux et al., 2012).

Synapse formation continues slowly until the 26th week when it accelerates resulting in a six-fold increase of synaptic density from 28 weeks PMA until 16 months of age. It then slows down again until adulthood. The first synapses have been found in the spinal cord at eight weeks PMA and in the cerebral cortex at nine to ten weeks PMA (de Graaf-Peters and Hadders-Algra, 2006). In weeks 24 - 32 there is growth in the thalami-cortical fibres into the cortical plate. In weeks 33 - 35 there is further synapse formation in the deep portion of the cortical plate (Yu et al., 2016; Kostovic and Jovanov-Milosevic, 2006).

Between the ages of 24 and 40 weeks there are several developmental events that are taking place. These include development and maturation of the preoligodendrocytes, microglia, axons, subplate neurons, germinal epithelium of the ganglionic eminence, thalamus, cortex and cerebellum. The preoligodendrocytes are the precursor cells to oligodendrocytes which make the myelin sheaths that allow synapses to move faster down the axons (Kugelman and Colin, 2013; Kanold, 2009). Glial cells are responsible for the formation of myelin, clearance of excessive neurotransmitters and regulation of the surrounding extracellular environment. Glial cell proliferation peaks from 40 weeks to one year of age and continues till an average of 40 years of age with the intra-cortical connections amongst the last for myelination (Girard et al., 2007). In a study conducted in 2006, magnetic resonance imaging (MRI) done on pre-term and term infants showed oligodendrocyte and axonal abnormality that was widespread throughout the cerebral white matter in the pre-term brain (Counsell et al., 2006). In the premature brain, there is minimal myelinated white matter. Between the weeks of 35 and 41, there is a five-fold increase in this myelination (Kinney, 2006). Microglia form part of the CNS protection to stop inflammation occurring to the brain tissue. If this development is interrupted the blood-brain-barrier can be affected causing inflammation to the tissues. Axons carry synapses to the rest of the body from the brain. If these are damaged the messages to the motor portion of the muscles can be damaged causing motor deficits. The neurons in the subplate respond first to sensory information and are important for the thalamocortical connections (Kugelman and Colin, 2013; Kanold, 2009).

Sulcation of the brain changes dramatically between weeks 18 to 34. The parieto-occiptal fissure is present at 18 weeks and is well-shaped. The calcarine fissure starts to fold at 24 weeks but is only definite at week 30. The central sulcus is seen at the brain surface at week 24 but only shows its normal orientation at week 35. The post-central sulci are seen on the surface at week 27 but are only deep at week 35 (Girard et al., 2007). A study conducted in 2007 showed that there was a link between cortical folding and PMA (Biagioni et al., 2007). This accounts in part for the increased risk of neurodevelopmental problems that can occur up to those specific ages. The cortical volume in the late pre-term infant at 34 weeks is only 53% of the term volume. This means that in the last six weeks of gestation there is still approximately half of the cortical volume still to develop (George et al., 2015; Kinney, 2006).

Chemical neurotransmitters such as acetylcholine, catecholamine, gamma-aminobutyric acid (GABA) and glutamate are present from eight weeks PMA on average. The main period of over-expression has been shown to be between week 12 PMA to two months postnatal age. GABA has been shown to be an excitatory neurotransmitter in early foetal development and then switches to the permanent version as an inhibitory neurotransmitter during the last trimester. Studies using Electromyography (EMG) investigation in premature children have demonstrated that there is a disruption in the monoaminergic systems which may be part of the cause for the dysfunction in the motor system often experienced by low-risk pre-term infants. Stress during the pre-term stage may be one of the explanations as to why low risk pre-term infants may suffer from motor, cognitive and behavioural problems. Developmental programmes support the infant in encouraging the infant's system to regulate against the increased energy expenditure and calorie use, and allow for a minimisation of stressful event (Vandenberg, 2007). Due to the over-expression of the catecholamine system until 44 weeks PMA it is suggested that therapeutic intervention be restricted until then to diminish the stress effects on the infants (de Graaf-Peters and Hadders-Algra, 2006). The effects of early intervention will be discussed later.

The above shows that depending on the gestational age at birth, there can be a disruption in central nervous system development. This can lead to various neurodevelopmental delays presenting in the child at a later age.

2.5.2 Musculoskeletal Development

Limbs first form as mesenchymal cell buds and are covered by ectoderm along the anteroposterior plane. These cells then condense the bud core and this becomes the location of the future skeletal structures. In the proximal forelimb bud the future humerus, radius and ulna condensation appear. The cartilage cells that emerge form a cartilage template. This template is replaced by bone via endochondral ossification (Shea et al., 2015). Skeletal and joint tissues are also derived from the mesoderm layer in the embryo. Mechanoreceptors in the joint capsules are formed between weeks five and eight (Sweeney and Gutierrez, 2002). At the joint interzones, cells are formed in three areas. These areas later form the permanent articular epiphyses and the intervening joint cavities become encapsulated with a synovial membrane. From this we can see that the formation of the skeletal system involves a coordinated endochondral ossification, differentiation of permanent structures and the development of the associated structures such as tendons, ligaments and menisci (Shea et al., 2015).

The clavicle and mandible ossification occur at eight weeks according to an ultrasound study. Ossification of the appendicular skeleton, ileum and scapula occurs at 12 weeks. The metacarpal and metatarsal ossification occurs from 12 to 16 weeks gestation. The secondary ossification centres are seen to be present from 29 weeks gestation (Nemec Stefan et al., 2012).

The movements of the foetus influence joint moulding and this continues throughout infancy and early childhood. This also allows the refinement of the joint proprioception. The mechanical forces that are generated during any foetal movements aid in the development of the shaping of the joints (Verbruggen et al., 2016; Sweeney and Gutierrez, 2002). The movements of the foetus can be seen via ultrasound by eight weeks gestation and felt by mothers from 15 weeks gestation (Verbruggen et al., 2016).

2.5.3 Motor Control

Motor control can be defined as an area of science the investigates how the central nervous system (CNS) is able to produce purposeful, coordinated movements as it interacts with the rest of the body and the environment (Latash et al., 2010). These movements can range from a simple reflex loop to a complex neuronal pattern that uses the entire CNS and peripheral nervous system (PNS) (Roller et al., 2012). Motor control uses the systems in the human body that function together to allow for balance. The primary systems involved in balance are the sensory system giving feedback, the motor system creating the movement and the biomechanical system including the bones and joints allowing for the frame to be held (Gaerlan et al., 2012).

The first motor control theory that will be discussed is that of the Reflex Theory which was proposed by Sherrington in 1906. He later published it in a book in 1920 (Sherrington, 1920). This theory states that movement is controlled by a stimulus-response and that reflexes are the basis for all movements. He stated that reflexes are combined into actions to create behaviour. He described his theory in terms of compound reflexes and their combined actions, where a stimulus causes a response which in turn is the stimulus for the next response. The clinical implications of this include that we can use sensory input to control motor output (Cano-de-la-Cuerda et al., 2015; Roller et al., 2012).

The Motor Program Theory was developed in 1976 by Schmidt (Schmidt, 1975). This theory states that movement is organised centrally. Signals are controlled through the afferent and efferent systems and allows the nervous system to plan movement. This theory uses the idea of recall memory to produce movement and recognition memory to evaluate response correctness. This theory investigates the physiology rather than the nature of reactions (Cano-de-la-Cuerda et al., 2015; Roller et al., 2012; Schmidt, 1975). This is clinically important as it helps patients relearn correct actions and retrains movements for important functional tasks (Roller et al., 2012).

The neuronal group selection theory (NGST) described motor development to have two phases of variability, being primary and secondary. During the primary variability phase motor behaviour is characterised by abundant variability which has been brought about by explorative motor activity of the nervous system. This exploration

causes the production of self-produced afferent information which shapes the nervous system. The secondary stage is described as the variability stage. This stage is said to be based on an individual's trial and error of movement. NGST has shown that accumulating sensorimotor experience plays a pivotal role in motor development. The developmental changes that occur in the nervous system are structured on the continual interaction when experience and genetics work together for improving motor skills refinement (Hadders-Algra, 2010; Edelman, 1989).

2.5.4 Motor Learning

Motor learning is defined as "an array of internal processes associated with practice and experience and which, in the context of acquisition of a specific skill, will produce relatively permanent changes in how motor activity is elicited" (Cano-de-la-Cuerda et al., 2015). It has also been found that higher levels of task relevant motor variability predicted faster learning (Wu et al., 2014a). There is no single theory that can explain how motor learning occurs but each theory can grant us a better understanding into the complex process (Zwicker and Harris, 2009).

The Fitts and Posner three stage model (Fitts and Posner, 1967) suggests that there are three main stages that occur during motor learning. There is the cognitive stage, where a new skill is learnt. This has been said to be the phase where the movements are visualised. Then there is the associative phase where the person performs this task in a specific task-orientated situation. The third stage is the autonomous phase where the task can be conducted in various settings and control is maintained throughout the task (Cano-de-la-Cuerda et al., 2015; Zwicker and Harris, 2009).

Bernstein in 1967, described his three-stage model which places the emphasis on the number of independent movements that are needed to complete an action as being the main requirement for learning a new motor skill (Bernshtein, 1967). This model of motor learning has three stages. The first is when the person simplifies their movements by reducing the degrees of freedom. The second stage is known as the advanced stage. During this stage, the person gains a few degrees of freedom which allow movement in more of the articulations involved in the specific task. The last stage is known as the expert stage. This stage possesses all the degrees of freedom that

are required to carry out the task in a coordinated way (Cano-de-la-Cuerda et al., 2015; Latash, 2010).

In 1972, Gentile proposed a two stage model for motor learning (Gentile et al., 1972). The first stage is an understanding of the purpose of the task, the development of movement strategies that are needed for the task and the interpretation of the environment that is needed for completing the task. The second stage looks to redefine movement to develop the capacity to adapt movement to changes to perform the task effectively (Cano-de-la-Cuerda et al., 2015).

The process of selecting an appropriate motor response to a situation is based on motor learning and not conscious decisions and occurs at various neuronal organization levels. With this interaction between the primary and secondary variability, the long-lasting developmental processes in the brain, such as dendritic refinement, myelination and synapse rearrangement, which allow for new neuromotor possibilities occur well into adulthood. Developmental changes in a young brain have been shown to have a large impact on motor behaviour and express as atypical motor development. Atypical motor development may be expressed as developmental delay in milestone attainment. This atypical development is shown as limited variability (Hadders-Algra, 2010). Investigations into white matter plasticity have also been done. There was strong evidence that showed white matter structure altered as a result of motor learning showing that early intervention can be very useful for premature infants (Roberts et al., 2013).

There is little research on the motor learning strategies in pre-term infants. It has been stated that pre-term infants are not as efficient in adapting their behaviour and movement to meet a specific task need and would therefore require assistance in learning this skill (Dusing and Harbourne, 2010). A large portion of research has been conducted on the normal development of infants and children. This research documents the process from conception to adulthood. This research has included the effect of different demographics, medical history and circumstances.

2.6 Motor Development

Motor development is defined as the process where a child acquires new movement patterns and skills (Malina, 2004; Clark and Metcalfe, 2002). This process needs to be continually modified through various systems including neuromuscular maturation, physical growth of the child, residual effects of previous movement patterns and lastly new movement experiences (Malina, 2004).

The Dynamic Systems Theory was proposed by Thelen in 1987 (Thelen, 1995; Thelen, 1989). This theory states that movement patterns self-organize depending on the environmental conditions. It places less emphasis on the CNS control and more on the physical explanations for the movement. This theory states that movement is the result of the environmental impacts on the system with the combined systems influencing each other. This is important clinically, as this theory takes velocity into account. The theory states that by increasing the speed of a movement, more momentum can be obtained allowing easier movement. It suggests we assess individual components, such as the musculoskeletal system for the deficits (Cano-de-la-Cuerda et al., 2015; Roller et al., 2012; Zwicker and Harris, 2009; Spencer et al., 2006; Thelen, 1995). In the Dynamic Systems Theory (Thelen, 1989), motor development is thought to be based on a feedback process due to interaction in the various body systems and the environment. This theory shows how each new developmental stage occurs due to numerous body systems merging in a certain way to allow the new development to occur (Campbell et al., 2011). This theory is based on four concepts. The first is the emphasis on time. Each new developmental task that is learnt sets the platform for the next task that is learnt. The second concept is that each task is due to multiple subsystems working together to allow the new movement to occur. The third concept is that the perception, action and cognition work together and not in isolation. There is never just a motor movement in isolation but there will always be a cognitive or emotional connection. The fourth concept is that of individuality. This shows that each child develops at their own pace and in a unique manner (Spencer et al., 2006).

Motor development in a child is not a linear process. There are both genetic processes and experiences that play a role. Healthy children demonstrate motor patterns that are

flexible, adaptable and dynamic (Oberg et al., 2012)**.** The development of motor skills during infancy and childhood is dependent on growth and maturation of the child including morphological, physiological and neuromuscular components (Venetsanou and Kambas, 2010).

Motor development has been used as the best indicator of a child's developmental status (Einspieler et al., 2008; Santos et al., 2001). The detection of problems in motor development during the first year of age has shown a high predictive value for problems in the medium and long term of premature infants lives (Kayenne and Linhares, 2011). Infants with motor lesions move differently compared to other infants. All typically developing infants have a normal array of fidgety movements known as general movements (Hadders-Algra, 2018). These movements are generated via the cortico-spinal fibres and the basal ganglia and cerebellum. When there is a motor lesion present these movements are absent and therefore the infant moves in a different manner when compared to children with no brain lesion (Einspieler et al., 2008).

2.6.1 General Movements

General movements (GM) are found from an early gestational age in the foetus. In humans, these complex movement patterns have been seen from eight weeks PMA. They are present in infants until five months of age when voluntary motor activity comes into use. The characteristic general movement patterns emerge at nine to ten weeks PMA (Hadders-Algra, 2018). General movements show variability (Einspieler et al., 2016; Peyton et al., 2016; Spittle et al., 2013; Hadders-Algra and Prechtl, 1992). They involve the head, limbs and trunk which move without a specific sequence. General movement assessment has been shown to be a reliable tool in predicting the brain function of infants and can be used to predict neurodevelopmental outcome (Ma et al., 2015).

General movements involve the entire body in various sequences involving the neck, arm, trunk and legs. They vary in speeds, intensities and range of motions. There are rotations around the limb axes that cause the movements to seem fluid (Einspieler et al., 2016). They are generated by a neural network located in the brainstem. To allow

the variability, the supraspinal projections activate, inhibit and modulate the activity of these movements (Einspieler et al., 2016). The occurrence of these GMs at eight weeks PMA correlate with the development of synapses in the spinal cord, which start to occur at six weeks PMA and speed up during week seven PMA (Hadders-Algra, 2018).

Movement in utero has long been studied but as technology has improved this can be better assessed and studied. The first recorded movement is a lateral flexion of the head at eight weeks PMA. Between nine and ten weeks, complex, generalised and startle moments start occurring. These include whole body movements of all limbs, trunk and neck. Local and isolated movements of arms and legs emerge at week ten. The act of hiccups also starts at ten weeks. This has been shown to be caused by a repetitive, short contraction of the diaphragm. At 11 weeks, the head of the foetus becomes mobile with flexion, extension and rotations occurring. At the same time, hand-to-face movements begin but are accidental. Breathing, stretches and yawn movements begin at 12 weeks. Positional changes become frequent and can be up to 25 times per hour in the first half of pregnancy. As the foetus grows these changes become less frequent. The alternating leg movements that occur continue postnatally as newborn stepping. The majority of foetal movements develop early in pregnancy and refine as the pregnancy continues and postnatally (Hadders-Algra, 2018; Einspieler et al., 2016).

The presence of poor variation of GMs at one month post-term, predict lower neurodevelopmental outcomes at two years. Abnormal fidgety GMs were shown to be an early marker for complex minor neurological dysfunction at puberty. Cramped-synchronized GMs and absence of fidget movements predict CP. For these reasons GMs can be used as a tool for early prediction of neurodevelopmental outcome in high risk infants (Ma et al., 2015; Spittle et al., 2013). GMs at one and three months show a significant relationship with the extent of white matter abnormalities at term-equivalent age in infants who were born very pre-term. IVH and PVL also showed a significant relationship with GMs at one and three months. The quality of GMs were shown to correlate with MRI findings in children with CP (Spittle AJ, 2008).

These GM have been shown to be an expression of the developing brain and form the cornerstone of early motor development (Hadders-Algra, 2018). The GMs change from writhing movements to fidgety movements at approximately three months (Einspieler et al., 2016). As these movements are being generated as motor patterns it reasons that these movements will develop into learned responses of motor development and motor learning, as they are said to the first co-ordinated movements our bodies conduct (Einspieler et al., 2016)

2.6.2 Gross Motor Development

Gross motor skills are defined as activities that use large muscles to move the trunk or limbs and control posture to maintain balance (Dodd, 2017). These skills begin developing in utero and continue throughout life.

Motor activity of a newborn continues the growth from the pre-term development. This comes in the form of reflexes and reactions. These reflexes can be primitive or postural. Primitive reflexes develop from birth and start to decline from three months when the cortical inhibition from the brain starts to occur. They are prompted by a specific stimulus. Primitive reflexes are brainstem-mediated automatic movement patterns. They begin to show from 25 weeks PMA and are fully present in full-term infants (Futagi et al., 2012; Malina, 2004; Zafeiriou, 2004). Postural reflexes develop from three months and increase in strength (Futagi et al., 2012; Malina, 2004). Postural reflexes are motor responses to a number of stimuli with the joints, tendons, muscles, skin, inner organs, telereceptors, otoreceptors and the labyrinth. They are shown to be specific postures of the trunk, head and extremities. These reflexes emerge at various ages and are thought to be a sign of a maturing central nervous system (Zafeiriou, 2004).

Postural control is another aspect of gross motor development that plays a huge role in children. The postural system is linked to all the CNS centres that control muscular tension, process sensory information and coordinate movement motor responses. The pyramidal system sends the plan that was generated in the cortex. This system controls both the complex posture involving voluntary control as well the movements of the arms, hands and fingers (Viholainen et al., 2006; Assaiante et al., 2005).

Postural stability is defined as the ability to maintain the centre of mass in relation to the base of support to prevent falls and complete the desired movement (O'Reilly et al., 2011). Balance is defined as the body's ability to maintain its centre of mass over its base of support and is the process where postural stability is maintained (Sheehan and Katz, 2013; Westcott SL, 1997). Postural control is the controlling of the body's position for numerous purposes. Those are the orientation between body segments, stability of the centre of mass in relationship to the base of support, preparation for movement and lastly, reaction to an internal or external force. Postural control is therefore a dynamic process that supports interaction with the environment or task (O'Reilly et al., 2011; Dusing and Harbourne, 2010). Static balance is whilst in a stationary position while dynamic balance is in a mobile position. Postural control is classed as an important and necessary motor ability. Children with many types of disabilities, ranging from learning disabilities with mild motor problems to cerebral palsy with more severe motor problems have been shown to suffer from poor postural control. This ability has been said to reach maturity by age seven years (Boonyong et al., 2012).

The first two years of a child's life are devoted to the attainment of developmental milestones. A developmental milestone is a term used to show the attainment of a specific voluntary skill using motor control coordination (Malina, 2004). These skills include postural control, locomotion and fine motor skills. Developmental milestone attainment usually occurs in a uniform pattern but this is not always the case (Malina, 2004). Voluntary movements begin during the first six months. There are three general principles of development. They are cephalocaudal development, proximodistal development and differentiation (Malina, 2004).

Cephalocaudal development is the principle where development occurs from the head downwards. It is seen as the coordination of movement that begins in the first six months with the head and neck, arms and hands. The next six months is the development of the trunk, arms and legs (Dodd, 2017; Law et al., 2014; Kanagasabai et al., 2013). The proximodistal developmental principle works in conjunction with the cephalocaudal developmental principle. This principle states that motor development

occurs from the centre of the body outwards to the extremities. For example, coordination begins with the upper arm, then forearm and then hands and fingers (Dodd, 2017; Law et al., 2014). The Dynamic Systems Theory shows that there are deviations to these patterns (Law et al., 2014; Roller et al., 2012). The principle of differentiation states that motor development occurs from general to specific movements. It states how development initially involves the entire body but over time these reactions become less generalised and more purposeful (Dodd, 2017; Clark and Metcalfe, 2002).

Independent walking is seen as the major developmental milestone during the first two years of an infant's life. The stages that allow this milestone to occur are a series of postural changes. The general sequence required is head control, upper trunk control and upper extremity control. Control of the trunk allows for independent sitting postures, initially with support followed by unassisted sitting (Malina, 2004). According to a study conducted by the World Health Organisation (WHO) during a multicentre growth reference study, they found that children conformed to the cephalocaudal principle of development occurring down the trunk as the infant develops postural control to allow unsupported sitting. The mean result for unsupported sitting was 6.0 months (±1.1) (da Costa Ribeiro et al., 2016).

Following this is the active progression into locomotion in the prone position of creeping and crawling on hands and knees at a mean of 8.5 months (± 1.7) (de Onis, 2006). Postural control of the legs by standing with assistance is the next phase at a mean of 7.6 months (± 1.4) (de Onis, 2006). Standing unassisted was shown to occur at 11.0 months (±1.9). This upright posture and movement pattern undergo refinement in the areas of balance and postural control and lead to unassisted walking at 12.1 months (±0.8) (Dodd, 2017; de Onis, 2006; Malina, 2004).

Gait is an important motor milestone that requires perception, spatial awareness, cognition and the motor system to work together. The gait pattern is refined continuously until a mature gait pattern is obtained (Jeng et al., 2008). There are five characteristics that determine a mature gait. They are cadence, velocity, duration of single support phase, step length and the ratio of the pelvic to ankle spread (Hillman

et al., 2009). The initial immature gait pattern is characterized by short and quick steps with the toes pointing outwards. Associated with this is trunk oscillation (Bosch et al., 2010). Postural control is of the utmost importance to the gait pattern (Kraan et al., 2017). The upper limbs are held in a rigid high-guard position allowing the toddler a wider base of support. There is also flat-footed contact with the ground unlike in adults where there is a heel-strike (Bosch et al., 2010). As the child ages, the gait variables will change. This includes the diminishing width of the base of support as the child's balance improves. There is then reciprocal arm-swing as well as an increase in step length, walking velocity and single-limb stance (Kraan et al., 2017; Vaughan, 2003). A more mature gait is achieved at approximately two to two and a half years of age (Kraan et al., 2017). There is said to be three different stages of stride development. The first being from three to four years of age, then from five to six years of age when children are able to modulate their strides. The final stage is said to be from age seven where children are able to show a mature stride length and ability to adjust this for various activities (Jeng et al., 2008). It has been documented that areas of cadence, stride length and base of support all affect the velocity of gait. These areas are said to only be fully developed in the teenage years (Kraan et al., 2017).

2.6.3 Fine Motor Development

Fine motor skills are defined as activities and skills that require coordination of small muscles to control small, precise movements especially of the face and hands (Dodd, 2017). The development of the fine motor skills is dependent on the development of normal vision (Goel and Gupta, 2012). As with gross motor, fine motor development also occurs in various stages.

From 36 weeks PMA, the infant's eye movements are present. By two months of age the infant is able to visually track objects in a lateral motion. By three months of age the infant is able to visually track objects in a circular motion. This ability is linked to their later fine motor movements of reaching and grasping (Dodd, 2017). As with gross motor development, this area of development has also been shown to follow a cephalocaudal and proximodistal pattern (Dodd, 2017). The three main stages of hand function are reaching, grasping and releasing. The development of reaching and grasping occur simultaneously from birth up till the sixth month for reaching and the

eighteenth month for grasping. Releasing starts developing from the fourth month and continues up till the eighteenth month (Dodd, 2017; Gallahue and Ozmun, 2006). In-hand manipulation develops from age one to seven years. It refers to the movement of an object in a person's hand (Rosenblum and Josman, 2003) .

It was observed that optimal hand functioning and stability mechanism are related. The correct posture allows infants to perform more movements through space. Changes in the position of the forearm changes grip strength. Poor postural control was shown to have a significant role on several developmental areas especially hand function (Rosenblum and Josman, 2003). It has been shown that the index finger plays an active role in grasping from as young as three months. The index finger usually contacts the object first and initiates the grasp reflex. This dominant role of the index finger becomes clearer with increasing age. After the initial index finger contact the remaining digits close together being controlled by the central nervous system for grasping and finger manipulation (Jovanovic and Schwarzer, 2011). The change from the use of the grasp reflex to active and voluntary grasping has been shown to occur between four and eight months of age. During this time the child will begin to use the thumb and move the hand in the best position to grasp the specific object (Dodd, 2017).

Postural muscle control is important in the development of fine motor ability. The development of trunk stability and central axis control is considered to be a necessity for upper limb function and hand usage (Rosenblum and Josman, 2003). It is said that postural stability is required for all motor actions whether fine or gross in nature (Viholainen et al., 2006). Every motor action can cause destabilizing actions and the child requires age-appropriate postural reactions to compensate for this (Dusing and Harbourne, 2010; Viholainen et al., 2006). With regards to the fine motor tasks of reaching and grasping, postural stability is very important. Reaching, grasping and manipulating objects requires dynamic stability of the shoulder girdle with a stable trunk. It also requires separate movements of the head and arms from the shoulders (Rosenblum and Josman, 2003). This is especially true of head control with regards to reaching and manipulation (Viholainen et al., 2006; Assaiante et al., 2005). The development of independent sitting which is a gross motor function, allows the infant

new ways to use the hands thus allowing fine motor skills to develop and mature (Dusing and Harbourne, 2010).

Motor development has been documented by the numerous research studies to be a complex process throughout the developmental stages. Research has included various gestational ages, complications as well as socioeconomic statuses of children.

2.7 Cognitive Development

Cognition is defined as the mental action or process of acquiring knowledge and understanding, through thought, experience and the senses (Robbins, 2011).

The second half of gestation and the neonatal period has been shown to be the most important for the development of the various cerebral pathways. The time before the 24th week PMA is characterised by the thalamocortical afferents forming. Between weeks 24 and 32, the thalamocortical afferent fibres grow into the cortical plate. By weeks 33 to 35 there is the growth of the cortico-cortical pathways into the cortical plate. In the neonatal period, there is the cessation of the corpus callosum growth of interhemispheric fibres. In the first postnatal month, there is an increased growth of synapses in the brain. This allows for cognitive development to occur in the infant (Kostovic and Jovanov-Milosevic, 2006). Cerebral changes during the last few weeks of gestation and the first post-natal months are vast. This growth and maturation is varied dependent on the region of the brain (Dubois et al., 2014). The thalamocortical pathway is the main route for sensory input to reach the cerebral cortex through the thalamus receiving these sensory inputs and sending them to the specific cortical areas for each sensory modality (Jose and Harvey, 2017). The cortico-cortical pathways are when neurons in one part of the cortex communicate with neurons in another part of the cortex (Roland et al., 2014).

The rate of maturation of the white matter in the developing brain cortex indicates an increased myelination of the axons. As the myelination increases it allows for more efficient neural transmission and thus faster information processing. By increasing the connections between the various cortex regions, the brain increases the amount of

fibres added to the white matter tracts which has been shown to have an improved cognitive functioning (Roberts et al., 2013; Paterson et al., 2006).

The cerebellum plays a role in cognition in executive, visuospatial and verbal functions. It was also shown that the cerebellum plays a role in achieving new cognitive tasks. This would therefore play a large role in the cognitive development of infants as the tasks they are learning are all new to them. Children who suffer from posterior fossa cerebellar malformations have been shown to display attention deficits and visuospatial problems. Cerebellar dysfunction from birth has been shown to cause cerebellar dyslexia leading to phonological, speed and literacy problems by having problems with articulation and memory. Children suffering from ADHD were shown to have smaller vermal volume of the cerebellum as well as problems in the frontal lobe showing the cerebellar-frontal connections to be prominent (Steinlin, 2007).

The cerebellum has also been shown to have a role in learning and memory. Working memory is a cognitive function that allows the temporary storage of information used to perform complex everyday tasks, such as reasoning and language comprehension. This is thought to occur through the cerebellar-frontal connection through the dentothalamic fibre tracts (Ben-yehudah et al., 2007). Memory is the ability to store information and is considered a basis of cognitive function. Areas of the brain related to memory include the hippocampus, prefrontal cortex and the cerebellum (Rovee-Collier and Cuevas, 2009). Properties of the infant brain are shown to be too immature to encode, store and retrieve memories over a long-term period. This capacity depends on brain structures that are not mature until the end of the first year of life (Rovee-Collier and Cuevas, 2009). Infants who were observed were shown to be slower learners and faster to forget when compared with adults (Hadders-Algra, 2018). This shows that memory is a developing process. An area for future research is that of memory retain related to an infant's age (Rovee-Collier and Cuevas, 2009). The cerebellum has been shown to have an increase in growth rate during the third trimester until three months of age. This explains why a child born prematurely during this crucial brain growth stage could lead to developmental issues in this area of the brain (Hadders-Algra, 2018).

Cognitive development is a life-long process of synapse building and various processes that occur in the central nervous system. The research conducted on this topic has shown how important early experience is in the various cognitive developmental pathways. An area of research that needs to be conducted in more depth is the link between cognitive and motor development.

2.10 Language Development

Language is essential for the human ability to think, communicate, remember and plan. The learning of language is multifaceted and begins in the womb (Levine et al., 2016). Hearing begins at the beginning of the third trimester. Sound is transmitted through bone conduction, from the amniotic fluid through the foetal skull and into the inner ear, allowing the foetus to hear and process language (Levine et al., 2016; Moon et al., 2013; Björn et al., 2012). During the first year typical developing children have formed patterns within language (Levine et al., 2016).

It has been documented that the language areas of the brain include that of Broca's area in the superior temporal gyrus, Wernicke's area in the superior temporal gyrus, parts of the middle temporal gyrus and the inferior parietal and angular gyrus in the parietal lobe (Friederici, 2011). The auditory function occurs bilaterally in the auditory areas of the temporal lobes. Syntax, or the rules of language occur in the temporo-frontal networks mainly on the left hemisphere. Sentence processing is supported in the temporo-frontal network on the right hemisphere (Friederici, 2011).

The cerebellum controls up to 100 vocal tract muscles involved in the production of speech. It also controls the rhythm and quality of speech, including loudness and pitch. Children suffering from posterior fossa tumours of the cerebellum were shown to suffer from ataxic motor speech problems, showing the level of control the cerebellum has on the speech muscles. Resection of these tumours has shown a 15% rate of speechlessness in children. Disorders of the cerebellum lead to a reduced maximum speaking rate, disrupted co-ordination of the laryngeal and orofacial movements and problems with speech timing (Ackermann et al., 2007).

Neonates are sensitive to rhythmic speech patterns and can distinguish their mother's native langue and voice over other adults speaking in the same language (Levine et

al., 2016). This was noted in a study on 30 neonates measuring pain while listening to their mother's voice. The results showed a decrease in stress and unstable vital signs. The neonates also showed a lower heart rate, better sucking rate and less crying (Azarmnejad et al., 2015).

Speech can be classed as the product of a complex series of processes. The formation of a simple phrase involves the formulation of a communicative goal, consideration of formality of speech, selection of vocabulary, the motor plan execution and intelligible articulation. This shows how involved the art of speech is. Due to this complexity in speech there are many areas where problems in speech can occur. These include the following: incorrect vocabulary, a hearing loss, a motor planning problem or a structural or neurological anomaly interfering with articulation (Weiss-Croft and Baldeweg, 2015; Powell, 2008).

Language development overlaps with both the cognitive and the motor aspects of development. Motor development plays a role in the oral motor control and coordination (Alcock, 2006). If a child shows a cognitive delay it has been reported that the possibility of a language deficit is higher (Ortiz-Mantilla et al., 2008). Language skills require muscle coordination of the lips and tongue in conjunction with the larynx and respiratory system. This shows how language and motor development is linked (Iverson, 2010). Motor development is also very important in the form of gesturing in the language domain. Another aspect where the two areas area also linked is that they both require repetitive motions. Motor control has also been shown to be required for the various positioning of the tongue and speech muscles (Alcock and Krawczyk, 2010).

Language development has been shown to have an impact on numerous areas of life for example feeding which is of utmost importance in the NICU. The connection between motor and language development needs to be explored in more depth with regards to the pre-term population.

2.11 Sensory development

There are seven documented senses that humans possess. These include two groups. The first group is that of the four distal senses: vision, hearing, taste and smell. The second group is that of three proximal or hidden senses: tactile awareness, proprioception and vestibular awareness (Foster and Verny, 2007a). A major contributing factor to neonatal development is that of how well the infant's sensory system integrates. This process is where the body is able to organise the sensation from the body and the environment (Foster and Verny, 2007a).

2.11.1 Auditory

The vestibule-cochlear provides the sense of hearing. The ear has three parts which are the external, middle and internal. The external air is the auricle and the external acoustic meatus. The middle ear is the air space, tympanic cavity and the temporal bone. The internal ear is the cochlea, which is a fluid filled labyrinth enclosed by the temporal bone (Graven and Browne, 2008a; Foster and Verny, 2007a). The external ear canal leads to the tympanic membrane. The middle ear houses the three bones-malleus, the incus, and the stapes. These bones connect to the tympanic membrane and allow for sounds waves to be transmitted to the cochlea (Graven and Browne, 2008a).

The sense of hearing begins to develop during the fifth week of gestation. This sense continues to develop until after the baby is born. Between weeks 10 and 20 of gestation, the inner and outer ear structures and 16000 hair cells form. By week 23 the foetus is able to respond to sounds and can indicate sound preferences. By 26 weeks gestation the foetus has learnt speech patterns, tone and rhythm of the mother's voice. By week 34 gestation the auditory threshold is at similar levels to that of an adult. The foetus is now able to develop a preference for certain sounds and can recognise neural language patterns and sequences of the mother's speech (Graven and Browne, 2008a; Foster and Verny, 2007a). This applies whether the child spends the last tem weeks of gestation in utero or born prematurely in the NICU and explains why there can be interference in this system in a premature infant (Graven and Browne, 2008a).

2.11.2 Vision

Vision allows a baby to orient themselves to light, faces and objects. The main organ of vision is the eye. The eyespots form at 28 days gestation. The eye is derived from four cellular sources: neural ectoderm, somatic ectoderm, neural crest and the mesoderm. Vision develops from the outside inwards. The optic sulci, retinal and lens discs are visible at four weeks gestation. The lens indents and forms the optic cup and lens pit. The lens pit then closes to form the lens vesicle. At the end of the embryonic period the eye is fully formed. The optic nerve develops from the optic vesicle and is a fibre tract that connects the brain and the retina. The oculomotor nerve supplies the motor ability to the eye for visual tracking (Braddick and Atkinson, 2011; Foster and Verny, 2007a).

At two months gestation, the axonal connections form. Between weeks 14 and 28 gestation there are 100 million neurons that have formed for the visual system but that are not connected until later in development. During the last trimester, the foetus is able to see light through the amniotic fluid. This helps the rods and cones to develop in the eyes. The visual system is only fully matured by the middle of childhood when the final myelination has occurred (Ramenghi et al., 2010; Foster and Verny, 2007a).

2.11.3 Taste

This sense is found on the tongue, where the taste nerve endings are found. The mouth forms from the stomatodeum and is initially a facial depression. The cranial section develops into the mouth and pharynx. The tongue is formed from the stomodeal ectoderm. The taste buds erupt on the tongue at eight weeks gestation. At 13 weeks gestation, the buds are formed in the mouth. The foetus is able to taste the amniotic fluid by the fourth month of gestation. The trigeminal and glossopharyngeal nerves, provide general sensory innervations to the tongue (Ventura and Worobey, 2013; Foster and Verny, 2007a).

2.11.4. Olfactory

The nasal structures begin to form between weeks six and eight of gestation. The main olfactory system consists of olfactory epithelium at the apical part of each nasal cavity. The olfactory system develops rapidly by sending nerve fibres from the outside surface

of the embryo to the deeper brain regions. The nostrils form around seven weeks gestation. During the 13th week of gestation, the olfactory bulbs separate from the nasal cavity and the facial bones. The olfactory sense continues to develop postnatally (Ventura and Worobey, 2013; Foster and Verny, 2007a).

The olfactory sense is of importance to pre-term infants (Ventura and Worobey, 2013). A small randomised control trial conducted on pre-term infants less than 29 weeks investigated the effect of regular smell of milk on milk tolerance. The control group consisted of 23 participants and the intervention group, 28. The study found that the group who were exposed to the smell of milk tolerated full enteral feeds quicker and showed a significantly improved weight gain percentage (Beker et al., 2017). This study, though small, demonstrates the importance of the olfactory sense, and the need for further investigation.

2.11.5 Tactile

This is the earliest sense to develop in utero. This sense includes that of touch and pressure. It is recorded to be the most mature sense at full-term birth. By three weeks post-conception, the tactile system begins to develop. By week five of gestation, the embryo can sense pressure to its lips and nose. This further develops and by week nine the embryo's arms, chin and eyelids can sense pressure. By ten weeks gestation, the legs have also developed the ability to sense pressure. The last body areas to develop this sense are that of the back and the top of the head. These areas only develop this sense post-birth. This has been said to decrease pain felt during childbirth (Tredgett, 2015; Foster and Verny, 2007a).

Skin is the organ that perceives pressure. The nerve receptors for this tactile awareness are found in the skin. During the late embryo and early foetal stages the skin on the palms, soles and the digits form. The ridges between the digits are evident from 12 weeks gestation (Foster and Verny, 2007b). This tactile system has two functions. These are to provide protection and to sense input. The perception of pain is said to be evident from seven weeks gestation. At 14 weeks, the body responds to touch and during the fourth month of gestation the sensory-motor portion in the brainstem begins processing pressure (Foster and Verny, 2007b). This system allows

infants to discriminate between objects. This ability refines after birth through experience of deep pressure and light touch. This is important for the manipulation of objects later in the child's life (Foster and Verny, 2007a).

2.11.6 Proprioception

Proprioception is the body's position sense. Proprioceptors are found in muscles, tendons and joints. These receptors allow information of awareness of where the body is in space. This allows coordinated movements used with the correct amount of force. It is also linked to the vestibular system (Tredgett, 2015; Foster and Verny, 2007a; Feldman and Eidelman, 1998). These receptors begin to form in the joint capsule between weeks five and eight. These receptors aid to the foetal movements which allow for joint moulding in utero especially during the third trimester (Sweeney and Gutierrez, 2002).

2.11.7 Vestibular

The vestibular system helps the body to respond to movements of the head and body. It allows for a sense of balance. It is located in the bony labyrinth. There are three structures that comprise this system. They are the semi-circular canals which conduct the speed and direction of movement; the saccule and utricle conduct the direction of gravity and linear movement (Tredgett, 2015; O'Reilly et al., 2011; Foster and Verny, 2007a).

Balance and equilibrium begin to emerge from five weeks gestation. Between seven and 14 weeks gestation the axonal fibres form the tiny hairs in the ears. These cilia support the neuronal connection and send information to the brain. The vestibular nerve is slowly myelinated, and this continues to occur until the ages of ten to 15 years. By month five, this system is functioning. The rapid maturity that this system undergoes is said to be the cause as to why this system is the most vulnerable to damage (O'Reilly et al., 2011; Foster and Verny, 2007a).

Sensory development is a complicated and multi-faceted developmental process. The research done has shown how the sensory system as a whole has an impact on most body processes.

2.9 The Effect of Prematurity on Development

2.9.1 The Effect of Prematurity on Motor development

Pre-term infants are more likely to suffer from motor co-ordination problems than full-term infants (Caesar et al., 2016; de Kieviet et al., 2009; Evensen et al., 2009). A study by Formiga and Linhares, (2011), showed that corrected age pre-term infants aged between one and 12 months showed lower motor scores than that of the normative values of full term infants on the Alberta Infant Motor Scale (AIMS) scores showing that pre-term infants are at risk for poorer motor outcomes. This was a cross-sectional study comparing 308 pre-term infants who weighed less than 2500g (Kayenne and Linhares, 2011). Premature birth interrupts the maturational process that is occurring in utero. Between the ages of 24 and 40 weeks there are several developmental events that are taking place.

The fragility of the nervous system which is not prepared for the extrauterine environment makes the brain vulnerable to insults. These include hypoxic injury the brain, inflammation, ischaemia, excitotoxicity and free radical attack (Caesar et al., 2016). These injuries can lead to numerous insults to the developing motor portion of the premature brain and can lead to motor developmental problems. The germinal matrix is a highly vascularised area of the brain. Premature birth can cause fluctuations in blood flow velocity and this can lead to venous congestion and haemorrhaging into the ventricles and surrounding white matter. This can lead to hydrocephalus (Caesar et al., 2016; Ballabh, 2010). Hydrocephalus is defined as an active distention of the ventricular system due to a malfunction between cerebrospinal fluid and its absorption (Faghih Jouibari et al., 2011). This ventricular enlargement can have very negative effects in the efficiency of the cerebrum as is causes its thickness to increase. Dilation of the ventricles causes the brain components to become progressively damaged. This damage occurs in a sequence according to the proximity of the neural tissue to the ventricles. The damage depends on the combinations of mechanical, ischaemic and metabolic disturbances. Periventricular axons are the most commonly damaged by hydrocephalus. These are the axons that carry motor and sensory information between the brain and the body which explains why there can be a motor developmental problem (Kugelman and Colin, 2013; Faghih Jouibari et al., 2011).

Neuroimaging studies have shown decreases in the growth of the basal ganglia and thalamus in premature infants. Basal ganglia injury can lead to movement disorders as the basal ganglia controls motor control and learning. Damage to the thalamus can lead to problems with motor signal relaying (Back and Miller, 2014).

It has been shown that the thalamus and the cerebellum are prone to pre-term injury and as these areas play important roles in cognitive, motor and perceptual tasks this can lead to developmental deficits in the motor development of the infant (Caesar et al., 2016). Studies have shown that pre-term infants perform lower on the gross motor standardized tests than full-term infants and this has been attributed to the possible decreases in volumes of the brain structures due to the pre-term birth (Allievi et al., 2016; Ball et al., 2012; Kayenne and Linhares, 2011; Evensen et al., 2009). Fine motor development has been documented to show lower scores in pre-term infants when a standardised test has been conducted on infants (Goyen and Lui, 2002). Fine motor scores have been shown to be lower in those pre-term infants who were born prior to 32 weeks, suffered from hyaline membrane disease or required longer periods of ventilation (Goyen et al, 1998).

The third trimester of pregnancy, which depending on gestational age, is either totally or partially missed, promotes the ideal flexion and midline position for the infant. The cramped uterus forces the infant into this ideal flexed posture and allows for rapid brain growth and midline orientation. It promotes the correct joint alignment and symmetry, promotes neuromuscular development and promotes self-soothing and sensory organisation (Madlinger-Lewis et al., 2014). Premature infants show increased trunk extension which can interfere with sitting postures and negatively influence mobility, as well as increasing the risk of asymmetry and poorer hand function (Madlinger-Lewis et al., 2014).

In a 2015 study it was shown that visual-motor integration problems can persist into adulthood for premature infants born with very low birthweight. It was stated that this appeared to be related to a reduced surface area of motor and visual brain cortices (Sripada et al., 2015). At 34 weeks gestation, the infant's brain only weighs 65% of a

term brain with the total brain volume increasing linearly with gestational age. The gyral and sulcal formation is not yet completed (Kugelman and Colin, 2013). This also shows how motor development can be affected negatively (Hirvonen et al., 2014). Infants who have delayed motor development show reduced postural control and may have atypical movement patterns which further increase the delay in the level of daily exploration which will further exacerbates the problem (Dusing et al., 2013).

With the increased knowledge of pre-term infant care, the survival rate of these children has increased. With this increase in survival has come a group of what are being referred to as ‘clumsy’ children. These children do not have a major disability but often suffer from deficits in motor control or developmental dyspraxia. These deficits can affect a pre-term infant regardless of gestational age or birthweight (Johnson et al., 2015). Late pre-term births are said to account for 75% of the pre-term population (Ballantyne et al., 2016; Figlio et al., 2016). Pre-term infants born in the late pre-term category have been shown to have double the risk of neurodevelopmental disability than term infants (Johnson et al., 2015).

Late pre-term infants are three times more likely to suffer from cerebral palsy than term infants due to the increased chance of PVL, placing them at a greater for motor problems (Kugelman and Colin, 2013). Infants born pre-term have been shown to be at a 10 - 15% risk of developing cerebral palsy and 40 - 50% have been shown to be at risk of minor motor and behavioural difficulties (George et al., 2015). The second half of gestation has been named the critical period for brain development. There are rapid changes in molecular, neurochemical and structural development in the brain. As the brain is still immature during this stage it can be damaged during these adverse conditions.

2.9.2 Impact of Prematurity on Cognitive Development

Pre-term children have been shown to suffer from cognitive impairments and academic difficulties at a much greater degree than their full-term counterparts (Allen, 2008). Intelligent Quotient (IQ) scores have also been shown to decrease with pre-term infants (Odd et al., 2012; Johnson, 2007). The prevalence of this has been shown to be in the range of 30- 40% for infants born prior to the 26 week gestation mark

(Anderson and Doyle, 2008). While prematurity can have negative effects on all developmental areas, cognitive impairments have been reported to be the most prevalent in the VLBW population (Linsell et al., 2015). Pre-term infants when tested at term age on functional MRI show reduced function between the cortex and the thalamus. This decrease in function is now seen as a critical risk for adverse neurocognitive outcomes due to the sensory-motor information that passes through the thalamus to the cortex (Back and Miller, 2014; Ball et al., 2012).

One of the greatest areas that pre-term children have shown to be at a disadvantage is that on spelling and reading. As the gestational age of the infant decreases, the difficulty increases (Allen, 2008). The poorer reading ability has been linked to a smaller axon diameter due to decreased myelination in areas of the corpus callosum, superior longitudinal fasciculus and inferior frontal-occipital fasciculus (Feldman et al., 2012). The corpus callosum is the main inter-hemispheric link between the left and right hemispheres of the brain. It transfers sensory and higher processed information via more than 180 million fibres (Dubois et al., 2014). Studies have shown that pre-term children are born with a smaller corpus callosum than that of full-term infants. This has been linked to lower cognitive scores (Allen, 2008). The damage is thought to occur due to hypoxic-ischaemic events or haemorrhages. The splenium of the corpus callosum has been strongly linked to IQ of a child. The splenium fibres connect the occipital and parietal cortices of the brain, as well as inferior and medical temporal regions (Knyazeva, 2013). Studies have shown that a splenium of a pre-term infant may be smaller than that of a full term infant which may lead to lower IQ scores in infants up to the adolescent age group (Allin et al., 2007). A larger corpus callosum and splenium show thicker myelination, and this improves the inter-hemispheric connectivity, which in turn improves IQ. As the myelination process is disrupted in a premature infant this can affect the child's IQ (Westerhausen et al., 2018). The superior longitudinal fasciculus is involved in language comprehension and production and is therefore involved in reading ability (Madhavan et al., 2014).

Premature children may have problems with mathematics, verbal working memory, perceptual and spatial organisation (Johnson, 2007). In a neuroimaging study conducted on premature infants, it showed that premature infants with calculation difficulties had significantly less grey matter in the left parietal lobe than those without

calculation difficulties. This area of the brain is said to be involved in the basic numeracy skills and this impairment may be the reason for poorer math skills (Simms et al., 2013). Studies have also shown that children who required longer periods of ventilation at birth show poorer mathematical skills than their peers that did not need such long periods of ventilation. This was found to be directly or indirectly due to stress and pain involved, the drugs used, or any hypo/hypoventilation and hyper/hypoxaemia experienced. The negative effects on general and specific mathematic skills have been explained by a neurodevelopment cascade. The adverse effects on general mathematical skills were linked to the poorer cognitive and concentration skills. The specific mathematic abilities were predicted by the duration of hospital stay and ventilation which suggests that early brain injury is a factor in these abilities (Breeman et al., 2017).

Abnormalities in the cerebellum are more characteristic of VLBW premature infants (Volpe, 2009). Children born pre-term have been shown to have cerebellar atrophy. Children born prior to 30 weeks are shown to suffer especially with injuries to the inferior hemisphere and vermis. Clinical features include: motor impairment, degrees of ataxia, athetosis or dystonia and significant developmental problem in the cognitive and speech domains. Pre-term birth also increases the risk of cerebellar haemorrhage, ADHD and behavioural problems all of which are common in pre-term infants (Steinlin, 2007). The cerebellum plays a role in cognitive, emotional and sensory domains (Casartelli et al., 2017; Stoodley, 2012). The cerebellum has connections with the prefrontal cortex of the brain that have cognitive functions. With regards to language, the cerebellum is associated with letter generation and phonological processing. If there is damage to the cerebellum in a premature infant this can lead to further reading difficulties. Memory is also a function of the cerebellum where it is involved in encoding and retrieval of memories. Damage here can cause a problem with cognition as this can lead to memory deficits (Stoodley, 2012).

2.9.3 Impact of Prematurity on Language Development

Language disorders have been shown to be present in three to 10% of term children while in premature infants it has been shown to be present in 30% of children (da Costa Ribeiro et al., 2016; Paquette et al., 2015; Ortiz-Mantilla et al., 2008). In a study done on 78 VLBW infants and 90 control infants at 36 months, they found that the

VLBW infants had lower scores in sentence comprehension than the controls (Montirosso et al., 2016). Pre-term children have significant and consistent differences in expressive and receptive language abilities on a number of different measures such as delays in the acquisition of vocabulary, quality of word use and syntax at two years of age. This has been said to be caused by the numerous brain injuries that can occur in a pre-term infant as well as the disruption in the myelination process that is interrupted (Montirosso et al., 2016; Mürner-Lavanchy et al., 2014).

There have also been problems reported with phonological processing at school age which shows the continuation of development from pre- and post-natal development. It also demonstrates the atypical developmental trajectory that can affect pre-term infants. In an MRI study conducted on an extreme pre-term population group, it was shown that premature infants retained the bilateral language network for a longer time period when compared to full term infants who show left-sided language organisation. This shows that there is an atypical language organisation in pre-term infants that can cause a delay in the neural language processing (Mürner-Lavanchy et al., 2014). There was no difference in the full-term control group. These results show that pre-term infants maintain an atypical bilateral language organization for a longer period than full-term infants. This may result in a delay in the neural language organisation in very pre-term infants (Mürner-Lavanchy et al., 2014; Guarini et al., 2009). The encephalopathy of prematurity causes impairment of growth of the cerebral grey matter of pre-term survivors and involves destructive disturbances. The grey matter abnormalities which are seen in children and adults who were born pre-term but who have normal neurocognitive function, still show altered cortical activation and functional connectivity during language and visual processing. This can explain why some pre-term infants suffer from language deficits without evidence of any severe brain injury (Back and Miller, 2014).

One in three premature infants has shown a delay in language acquisition at age three (Paquette et al., 2015). Delayed development of expressive and receptive language in preschool children impacts negatively on their interpersonal skills, social functioning and academic achievement due to the cognitive involvement of language development and the fact that the children cannot express themselves (Paquette et al., 2015). During the preschool years premature infants have demonstrated poorer vocabulary

and decreased language complexity. This has been shown to continue into school years as well (da Costa Ribeiro et al., 2016). Significant differences have been found between term and pre-term infants with regards to their receptive language which impacts on the cognitive development and IQ scores. Receptive language is an important aspect of information processing and for this reason language is seen as a sign of cognitive abilities and IQ (da Costa Ribeiro et al., 2016; Paquette et al., 2015).

Children born prematurely score consistently lower on standardised language measures with the major differences being in global language skills (Mahurin Smith et al., 2014). These academic difficulties have been shown to exist until the age of seven (McGowan et al., 2012). Early predication of language impairment is a major focus of developmental follow-up. Poor pre-reading skills and later school aged literacy, are three to five times more prevalent in premature children (Woods et al., 2014).

2.9.4 NICU and the impact on sensory development

Prematurity has been shown to increase the risk to the maturation of the sensory systems due to the interruptions of sensory developmental in utero. Much of the development and maturation of this system takes place during the last 16 – 20 weeks of gestation (Mitchell et al., 2015; Lucas-Thompson et al., 2008). It is also thought that the NICU causes an overload of sensory stimuli to the infant causing the physiological responses to lead to behavioural changes (Lucas-Thompson et al., 2008). A growing research base into the plasticity and experience-dependent characteristics of sensory organisation has highlighted that the pre-term infant is at risk and requires optimal sensory care (Lickliter, 2011).

Sensory systems have been shown to provide the platform for various learning experiences through infancy and for this reason sensory impairments can lead to neurodevelopmental problems (Philpott-Robinson et al., 2017; Chorna et al., 2014). Therapists have also stressed the importance of sensory modulation. This is the process of either increasing or decreasing neuronal activity to enhance or dampen response to sensory input. It has been reported that infants born pre-term suffer with sensory modulation difficulties the severity of which is linked to gestational age and

NICU length of stay (Jorquera-Cabrera et al., 2017; Philpott-Robinson et al., 2017; Chorna et al., 2014).

Sensory overstimulation and pain cause an excessive activation at the central afferent pain pathways. This causes an excessive N-methyl-D aspartate (NMDA) receptor activation causing excitotoxic damage. NICU stressors are associated with decreased brain size in the frontal and parietal regions, altered brain microstructure and functional connectivity in the temporal lobes. These destructive processes occur in an already insufficient self-regulatory sensory ability further decreasing the sensory system's functioning (Bröring et al., 2017).

There are numerous factors in the NICU which can add to the sensory stressors of a premature infant. These include the intense lighting, excessive noise and painful procedures (Cabral et al., 2015). In a cross-over and comparative study, conducted on 15 pre-term and 15 full-term participants, the relationship between sensory processing and motor development was studied. The participants were tested between four and six months of age using the Test of Sensory Functions in Infants and the Alberta Infant Motor Scale. The results showed no significant relation but all participants who had an abnormal score in the sensory test and presented with a motor score on the fifth percentile. This study has a small sample size and needs to be reproduced with a larger sample size (Cabral et al., 2015). When all these stressors cause overload in sensory stimuli, the physiological responses are altered. This leads to an altered state of rest, irritability, crying and decreased auditory response and motor development. This is caused by the lack of inhibitory control to process, organise and select the sensory input due to the brain's immaturity (Cabral et al., 2015).

Another sense that can be affected in NICU is proprioception. By performing specific movements of the limbs, it has been shown that physical activity can increase bone mineralisation and growth in infants in NICU (Jobe, 2014; Moyer-Mileur et al., 2008; Foster and Verny, 2007a). By optimising normal movement, proprioceptive input can be increased by increasing joint function which can aid in normal brain development (Whelan, 2014).

Another problem facing premature infants is that once born they no longer receive the tactile stimulation they would have experienced in utero. The sense of touch is the fastest-developing sense in an infant and this is important as these infants are often deprived of positive human touch (Abdallah et al., 2013). Not all touch to which the infant is exposed in the NICU is positive and may be overstimulating resulting in adverse physiologic and behavioural state responses (Smith, 2012).

At 25 to 26 weeks a loud noise in the NICU will cause changes in the autonomic nervous system of an infant. This includes the heart rate, blood pressure, respiratory rate, gastrointestinal motility and oxygenation. The cochlea and the auditory cortex in the temporal lobe of the brain are the most affected by developmental care and noise in the NICU environment (Jobe, 2014; Graven and Browne, 2008a).

Visual problems in premature infants have been linked to co-morbid brain lesions that affect the thalamus and white matter, such as PVL and IVH. Early exposure to the outside world can interfere with the visual field development in premature infants. This is made worse by the any brain lesion present (Ramenghi et al., 2010). Bright lights in the NICU have been shown to prevent premature infants from opening their eyes as much as term infants do and thus decreases their ability to take in their surroundings (Mitchell et al., 2015; Jobe, 2014).

The circadian system in mammals is controlled by the anterior hypothalamus. The foetal circadian rhythm has been shown to be synchronised by the maternal circadian rhythm. As the infant is away from the maternal influence due to the NICU admission, the pre-term infant has been shown to lose this rhythm after birth for up to three weeks and requires time to adapt to their own rhythm (Dorn et al., 2014). Sleep has been shown to be vital in brain development and the maturation process (Allen, 2012). The sleep-wake cycle develops into very distinct states as the neural structures continue to develop, and this is a necessary requirement for physiological mechanisms. If a pre-term infant cannot regulate this cycle it can cause the brain to develop incorrect behaviours in response to various stimuli such as light (Allen, 2012).

2.9.5 Effect of Drugs on Developmental Outcome

Various drugs are used on pre-term infants in the NICU. Sedatives and analgesics are used to minimise the effects of painful stimulation that the pre-term infants are exposed to. Sedative drugs alter the synaptic transmissions at the GABA receptors (Loepke, 2010). GABA receptors are integral to the early brain development as it has an excitatory function during neurogenesis, neuronal proliferation and differentiation of the brain development (Wu and Sun, 2015). When a pre-term infant is given sedative drugs this can then interrupt critical brain developmental processes (Loepke, 2010).

A commonly used drug in the NICU is that of postnatal steroids. Corticosteroids are used in this population group to treat bronchopulmonary dysplasia. The decision to treat a pre-term infant with corticosteroids is a difficult one as both the steroid treatment and the bronchopulmonary dysplasia have risks to the neurological development of the infant (Doyle et al., 2014). In a meta-regression analysis conducted in 2014 on 14 randomised control trials, it showed that infants who were at risk of bronchopulmonary dysplasia showed fewer cases of poorer neurological outcome following one dose of steroids (Doyle et al., 2014). In an older, randomised control trial conducted on 1721 infants, it reported that the infants who were diagnosed with poorer neurological outcome showed a slighter higher use of postnatal corticosteroids (Doyle et al., 2005).

From this section, the vast risk of developmental complications that can arise from prematurity is clearly documented. The timing of birth; medical history or maternal factors can have an impact regardless of any intervention done. This at-risk population group require close monitoring to ensure that they are able to reach the maximal quality of life regardless of any possible complication.

2.10 Early intervention

Early intervention (EI) should be provided for children who are classed as at risk for developmental disabilities. EI is a multidisciplinary approach provided for children from birth to five years to promote child health and minimise developmental delays. This is accomplished through individualised developmental and therapeutic services. This service is provided by physiotherapy, occupational therapy, speech therapy, developmental psychology and education specialists (Cioni et al., 2016). EI

programmes vary but they all share the same goal of preventing or reducing the functional impacts of impairments (Hilderman and Harris, 2014).

NICU-based EI programmes are usually intervention-based and focus on the environment to minimise stress for the infant in the NICU. These include programmes on sensory abilities, neurodevelopmental theory and parent-led intervention programmes (Spittle et al., 2015). This Cochrane review included EI programmes that began within the first year of life. The studies included had to be randomised or quasi-randomised controlled trials. Twenty-five studies met the inclusion criteria. This was a sample size of 3615 participants. The conclusion of this study documented that EI programmes for pre-term infants had a positive impact on both motor and cognitive developmental outcomes (Spittle et al., 2015). These programmes vary in the approaches that they use. Certain programmes are used whilst the infant is in NICU while others only begin on discharge from the NICU. Many of the programmes are aimed at using play therapy aimed at the developmental progress that the child requires depending on the age of the infant at the various testing ages in the various programmes. Many of the programmes involve the parents in the treatment, but these studies reported difficulty in monitoring the quantity and quality of the intervention given (Spittle et al., 2015).

The advantage of beginning intervention early is that the brain is believed to be plastic. This is especially true after the completion of neuronal migration during which the processes of dendritic outgrowth and synapse formation are highly active (Cioni et al., 2016). Neuronal migration occurs in humans during weeks 12 through 24. This results in the cortical plate being formed which keeps developing until five months of age. This allows the time for early intervention to begin in the NICU to ensure that the developmental interventions can take effect during this neuronal migration (Naumburg et al., 2012). The term brain plasticity refers to the capacity of the central nervous system to modify its structure and function. The normal brain has three plasticity types: experience-expectant, experience-independent, and experience-dependent (Kolb and Gibb, 2014). Experience-expectant plasticity occurs mainly during development. For the different areas of the brain to develop they require specific experiences to occur. Experience-independent is also mostly a developmental form of plasticity. This is

based on the brain's ability to form rough structures irrespective of experience. When cells fire together, they increase their connections. This plasticity type doesn't require external stimuli to occur and allows the nervous system more precision in connectivity. Experience-dependent plasticity shows changes in the brain that are required to modify neurons that are already present (Kolb and Gibb, 2014). Cortical function has been shown to build up on different neuronal connections. Experience is said to modify these connections by selecting the stable ones and removing the others (Fu and Zuo, 2011). The sensitivity to environmental stimuli on the neonatal brain is referred to as experience-dependent as the functional brain pathways are modified to response to the environmental stimuli and experience (Cioni et al., 2016). Even though this plasticity occurs throughout a person's life the young brain shows greater potential for modification due to the increased myelination and neural projections that are occurring at this age. Evidence of critical periods for visual, auditory, somatosensory and cognitive systems have been demonstrated in the young brain. This occurs due to the increased myelination at this age as well as the sprouting of more neural projections than in later years. This allows for more brain development and brain plasticity due to experience and environmental factors (Cioni et al., 2016; Fox et al., 2010).

When EI begins in the NICU it should focus on reducing the stress factors that these infants are under (Cioni et al., 2016). During an observational study conducted by Smith et al (2011), conducted on 55 premature infants, it was found that stress was the greatest during the first 14 days of life. It was also found that increased exposure to stressors in the NICU had a link to a decrease in brain size on the frontal and parietal region. There was also altered microstructure and functional connectivity within the temporal lobes (Smith et al., 2011). The neural network development in premature infants in the temporal lobes of the brain of the premature infant appears to be less mature as well (Benzies et al., 2013; Smith et al., 2011; Fox et al., 2010). Pain causes stress in neonates. The nociceptive stimuli reach the cortex and cause pain-specific activation and this alters the peripheral and central pain processing in neonates (Brummelte et al., 2012).

A systematic review carried out for pre-term infants, who are at increased risk for neurodevelopmental disorders, shows evidence that early intervention in the first

months of life has positive effects on early psychomotor development. These effects show a higher IQ score in the developmental group and improved balance and coordination scores (Spittle et al., 2015). EI has been shown to be critical in order to limit the negative consequences of prematurity for cognitive, academic and social functioning (Paquette et al., 2015; Spittle et al., 2015). Early prevention and intervention has been shown to minimize the negative impacts of prematurity on language development (da Costa Ribeiro et al., 2016). A systematic review looked at 25 different studies documenting early intervention programs provided to pre-term infants. The studies all used different programmes and for this reason cannot be compared with each other for effectiveness (Spittle et al., 2015). A different study conducted on 285 premature infants reported an improvement in the infants' general movements following an EI programme. The groups were each divided into 3 sub-groups: <32 weeks; 33-34 weeks; and >35 weeks. The intervention commenced on the third day of life and continued to the 54th week of life. The results showed that the intervention group had more fidgety movements. The interventions included playing music; looking at the mother's face; massage; oscillatory shaking; hydrotherapy with the child lying in warm water (Ma et al., 2015). This is an important result as general movements have been said to be predictive of an infant's neurodevelopmental status. The intervention strategies used in this study are all readily available but a long-term study is required to evaluate the long-term benefits (Ma et al., 2015).

Even though research shows that late pre-term infants have fewer risks than early pre-term infants their developing brains are still only 65% of the weight of a full-term brain and all the glial and white matter connections have not completely formed yet. For this reason late pre-term infants should also receive EI programmes (Shapiro-Mendoza et al., 2013).

Physiotherapy EI programmes focus on the infants' motor development. These programmes aim to optimize the motor development of the child (Spittle et al., 2015). These intervention strategies are aimed at modifying sensory input and abnormal movement patterns to help improve motor outcomes through active and passive techniques (Spittle et al., 2015). Interventions that optimise postural control and selective moments in pre-term infants may be important in decreasing the motor

development delay (Oberg et al., 2012). Postural control is needed for the development of movement strategies. Reduced postural control in infants born pre-term has been postulated to be related to reduced balance at six years of age (Ustad et al., 2016).

The way an infant moves and interacts during the early development shapes their understanding (Dusing et al., 2013). Movement allows for cognition-perception-action cycles. These are used by infants to increase their movement patterns and increase learning opportunities and improve development (Dusing et al., 2013). Motor development is dependent on experience and active participation. This causes synaptic connections to be refined and causes organization of the brain. Environments that are enriched with stimulation and targeted training strategies affect brain and corticospinal development by allowing the neural plasticity of the brain and experience-driven stimulation to occur. For this reason they are likely to influence motor development (Ustad et al., 2016). Pruning is the process of synaptic elimination (Salmaso et al., 2014). The brain undergoes lengthy development and differentiation of the subplate, alignment and layering of the cortical neurons. Selective pruning also occurs of the neuronal processes and synapses allowing the early intervention to take effect during this critical time period of brain development (Grunau, 2013).

Early intervention studies for pre-term infants in South Africa are difficult to come by. An area where early intervention in South Africa has been well documented is that of HIV. In a study conducted on 122 HIV positive toddlers, a home stimulation programme significantly improved both cognitive and motor developmental areas (Potterton et al., 2010). A large portion of children in South Africa grow up in poorer socioeconomic circumstances and this has been shown to significantly decrease their developmental outcomes (Samuels et al., 2012). Developmental screening in the public sector is the responsibility of the primary health clinics but developmental screening is not a legal requirement in South Africa. The Road to Health cards are used but due to poor staffing resources this is often not completed. One successful developmental screening clinic that is run as a follow up for pre-term infants is that of the clinic at Chris Hani Baragwanath Hospital. This is a multidisciplinary clinic where at-risk infants can be screened and referred on to the appropriate therapy. The private

sector have more efficient resources but the need for more multi-disciplinary therapy programmes was highlighted as a need (Samuels et al., 2012).

In table 2.1, an overview of EI research conducted in the pre-term population is presented.

Table 2.1 Studies on EI on the pre-term population

Citation	Study Design	Population	Intervention	Comparison	Main Findings	Conclusion
CIONI, G., INGUAGGIATO, E. & SGANDURRA, G. 2016. Early intervention in neurodevelopmental disorders: underlying neural mechanisms. *Developmental Medicine & Child Neurology,* 58**,** 61-66	Meta-analysis	Pre-term infant studies; animal studies	Combined data on the reported findings on neurodevelopmental intervention for various therapy types	Comparing the neural mechanisms described in various publications regarding EI	EI aids in the positive outcome developmentally but not in all cases studied; new forms of EI are emerging that require research	Early detection of underlying conditions is crucial for effectiveness of treatment; Further research is required for significant results regarding EI
MA, L., YANG, B., MENG, L., WANG, B., ZHENG, C. & CAO, A. 2015. Effect of early intervention on premature infants' general movements. *Brain and Development,* 37**,** 387-393	Randomised Controlled trial	285 Pre-term infants all less than 37 weeks gestation;	The intervention including: (1) auditory stimulation; (2) visual stimulation; (3) tactile stimulation; (4) vestibular motion stimulation; (5) pediatric gymnastics; (6) hydrotherapy	Comparing intervention group who received the programme to the control group who only had their feeding as the intervention group	No difference between groups regarding writhing movements; significant difference between groups regarding the fidgety movements	EI could improve fidgety movements in pre-term infants
OHLSSON, A. & JACOBS, S. E. 2013. NIDCAP: a systematic review and meta-analyses of randomized controlled	Systematic Review	627 Neonates (11 primary and 7 secondary studies)	Investigating the effectiveness of the NIDCAP programme	Comparing outcomes of morbidity and mortality at 18 months following	No significant differences between groups	No long-term or short-term benefits following the NIDCAP programme were found

trials. *Pediatrics,* 131**,** e881-93				NIDCAP intervention		
MCANULTY, G. B., BUTLER, S. C., BERNSTEIN, J. H., ALS, H., DUFFY, F. H. & ZURAKOWSKI, D. 2009. Effects of the Newborn Individualized Developmental Care and Assessment Program (NIDCAP) at Age 8 Years: Preliminary Data. *Clinical Pediatrics,* 49**,** 258-270.	Two-group Randomised controlled trial	38 <29-week gestation pre-term infants	- Intervention group: NIDCAP from admission to two weeks corrected age. - Control group: standard nursing care.	Comparing the effects of NIDCAP at eight years old on extremely pre-term infants	Significantly improved right hemisphere and frontal lobe function in the experimental group.	Results support the conclusion that NIDCAP has long lasting effects into school age
VIGNOCHI, C. M., SILVEIRA, R. C., MIURA, E., CANANI, L. H. S. & PROCIANOY, R. S. 2012. Physical Therapy Reduces Bone Resorption and Increases Bone Formation in Preterm Infants. *American Journal of Perinatology,* 29**,** 573 578	Randomised Controlled trial	30 pre-term infants <30 weeks gestation	Fifteen minutes of daily passive movements with gentle compressions five days a week	Data was taken relating to feeding, body weight, bone-specific, alkaline phosphate between the intervention and control group	Bone-specific, alkaline phosphate increased in the intervention group	Passive exercise and joint compressions should be included in the treatment for pre-term infants to aid in preventing metabolic bone disease

STALNAKER, K. A. & POSKEY, G. A. 2016. Osteopenia of Prematurity: Does Physical Activity Improve Bone Mineralization in Preterm Infants? *Neonatal Network,* 35**,** 95-104	Systematic review	562 Pre-term infants (12 Randomised controlled trials)	Investigating the literature regarding physical activity and the effect on osteopaenia	Comparing the outcomes using bone quality measures	The results documented that a daily passive movement with joint compression programme was able to improve bone mineralisation	This treatment technique is of benefit to be included in a NICU treatment care.
VICENTE, S., VERÍSSIMO, M. & DINIZ, E. 2017. Infant massage improves attitudes toward childbearing, maternal satisfaction and pleasure in parenting. *Infant Behavior and Development,* 49**,** 114-119	Longitudinal study	194 mother-baby dyads	Massage performed by mothers as taught to them by a physical therapist	Measures included: Self-reported measures regarding attitudes concerning motherhood; experience associated with motherhood; paternal satisfaction; separation anxiety	Intervention group showed more confident and better adjusted mothers.	Mothers who are taught to massage are more relaxed and adjusted to motherhood
SHOGHI, M., SOHRABI, S. & RASOULI, M. 2018. The Effects of Massage	Randomised Controlled trial	40 mother-baby dyads	Massage performed by mothers for 15 minutes per day for five days	Maternal-attachment outcome measure	Significant difference between the groups in favour of the	Mothers who massage their pre-term infants show improved maternal-infant bonding

by Mothers on Mother Infant Attachment. *Alternative Therapies in Health & Medicine,* 24**,** 34-39					experimental group	
MONTEROSSO, L., KRISTJANSON, L. & COLE, J. 2002. Neuromotor Development and the Physiologic Effects of Positioning in Very Low Birth Weight Infants. *Journal of Obstetric, Gynecologic & Neonatal Nursing,* 31**,** 138-146	Literature review	180 theoretical writings, studies and case reports	Literature review to assess the best effects of neuromotor development and physiological effects in very low birth weight infants	Studies were assessed for scientific rigour and comparisons made to find consistent findings	- Posture and mobility development in newborns require a balance between active and passive muscle tone - Prone position can lead to short-term and long-term postural and developmental problems	Positioning should be based on the child's gestational age and health status
VAIVRE-DOURET, L., ENNOURI, K., J RAD, I., GARREC, C. & PAPIERNIK, E. 2004. Effect of positioning on the incidence of abnormalities of muscle tone in low-risk, preterm infants. *European Journal of Paediatric Neurology,*	Prospective randomised control trial	60 pre-term infants between 31- and 36-weeks gestation	Intervention: position changed every three hours varying into all positions. In supine the child was position with a bolster to flex the knees Control: Prone position as standard practice suggests	Neurological assessments were done at 38 weeks	Control group showed dominance in the extensor muscles, hyperabduction and flexion of the arms and developmental delay.	Regular turning with correct physiological postures aids in preventing musculoskeletal and neurodevelopmental problems

8**,** 21-34						
BERGMAN, N. J., LINLEY, L. L. & FAWCUS, S. R. 2004. Randomized controlled trial of skin-to-skin contact from birth versus conventional incubator for physiological stabilization in 1200- to 2199-gram newborns. *Acta Paediatrica,* 93**,** 779-785	Randomised controlled trial	34 low birth weight infants; 1200g - 2199g	Intervention group: skin-to-skin with hips and arms flexed for the first six hours Control: Standard incubator care for the first six hours	Vital signs were monitored	All intervention group subjects were stable for six hours. 62% of the control group experienced hypothermia	Skin-to-skin contact allows for more stability with regards to vital signs in the first six hours when compared to conventional care
JUNEAU, A. L., AITA, M. & HÉON, M. 2015. Review and Critical Analysis of Massage Studies for Term and Preterm Infants. *Neonatal Network,* 34**,** 165-177	Systematic Review	14 articles met the criteria. Seven related to pre-term infants and seven to full-term infants	Articles assessed time massaged, oil or none and body parts massaged.	Outcomes looked at were sleep, weight gain and growth, bilirubin, blood circulation and parent-child interactions	Benefits for massage in the pre-term group included improved weight gain, decreased response to pain and increased interactions with parents	This review stated that there is not enough evidence to support massage in term or pre-term infants but should be looked at a case-by-case assessment

Table 2.1 documents an overview of EI research conducted in the pre-term population. This overview documents the vast differences in studies relating to gestational ages, techniques and outcomes. From this table, clear points are that techniques should be chosen based on the infant's medical status and needs as the benefits of EI are also varying between researchers. The various techniques used in the different studies were documented to show improvement in developmental scores, medically stability, and long-term musculoskeletal health.

2.13.1 NIDCAP

The Newborn Individualised Assessment Program (NIDCAP) was established in order to provide health care professionals with the training needed to care for pre-term infants (Als, 1986). The training for the NIDCAP programme can only be done at NIDCAP-approved centres by NIDCAP training supervisors (Als, 1986). It requires hours of training and is costly to complete.

In a small sample size study of 30 infants, a significant difference was documented in the NIDCAP group showing improved neurobehaviour, electrophysiology and brain structure of the group of IUGR infants (Als et al., 2012). This is in contrast to the large 627 infant systematic review conducted in 2013. This study found no evidence of any short- or long-term benefits of NIDCAP to the neurological development of pre-term infants (Ohlsson and Jacobs, 2013). A study looking into the length of stay for a pre-term infant while on the NIDCAP programme showed a 25 day difference in favour of the NIDCAP group for discharge. This study only included infants who were born at less than 32 weeks gestational age (Moody et al., 2017).

As seen, this program has shown varied results across research studies. There are currently no NIDCAP-approved training facilities in South Africa and for this reason it is a costly programme to undertake.

2.14 Kangaroo Mother Care

Kangaroo mother care (KMC) is defined as skin-to-skin contact between infant and mother (Conde- Agudelo and Díaz- Rossello, 2016). In this Cochrane review, the author documented that there is sufficient evidence to support KMC in stable LBW infants but the evidence for unstable LBW infants is inconclusive. The positive effects from KMC were found to be decreased maternal stress levels; a decreased risk of infection; improved breastfeeding rates; and improved weight gain (Conde- Agudelo and Díaz- Rossello, 2016). A study conducted on 300 pre-term infants documented significant results with regards to KMC and cognition and attention span later in life (Ropars et al., 2018).

A study conducted on 92 pre-term infants tested which KMC position was more effective for motor development. It was found that by the infant being placed in the lateral decubitus position, there were improved short term motor benefits but no long-term follow-up study was conducted. This position allows the infant to mimic physiological flexion whilst receiving the benefits of the act of KMC (Barradas et al., 2006).

2.14 Massage

Due to premature infants having extended stays in the NICU, they are exposed to various touch and handling stimuli and these can be painful and stressful (Abdallah et al., 2013). It has been that shown pre-term infants show greater sensitivity to pain compared to full term infants (Grunau, 2013).

It has been proposed that these painful and stressful treatments can play a role in altering the brain maturation process and therefore negatively impact the neurobehavioural outcomes of pre-term infants (Abdallah et al., 2013). When an infant attempts to adjust to these stressful situations, the hypothalamic-pituitary-adrenal axis is activated. This causes the change in the plasma levels of cortisol and beta-endorphins to reach its maximum (Altimier and Phillips, 2016; Asadollahi et al., 2016). Long term complications of high cortisol levels include insulin resistance, hyperlipidaemia, immunodeficiency and destructive changes to the hippocampus. As premature infants cannot adjust to environmental stress, interventions such as massage can be used to aid in the improvement of their autonomic nervous system functioning (Asadollahi et al., 2016).

Massage is defined as a systematic touch by human hands which stimulates the tactile sense of the infant to have positive effect on the infant (Abdallah et al., 2013). Massage has been used safely from as soon as the infant is medically stable in NICU (Brummelte et al., 2012; Grunau et al., 2006). Positive effects from massage that have been documented include increased weight gain, decreased pain responses, improved digestion, increased temperature, positive effect on heart rate variability, shorter length of hospital stay, improved circulation, reduced stress shown by lower

serum cortisol levels, enhanced immune system, less sepsis, improved neurodevelopmental scores, decrease bilirubin levels, and modified sleep patterns as shown by EEG power spectral density (Asadollahi et al., 2016; Lai et al., 2016; Basiri-Moghadam et al., 2015; Choi et al., 2015; Abdallah et al., 2013; Kumar et al., 2013; Wang et al., 2013; Smith, 2012; Field et al., 2010; Kulkarni et al., 2010; Diego et al., 2009; Massaro et al., 2009; Hernandez-Reif et al., 2007; Field et al., 2006; Lee, 2005).

Improved weight gain has been reported to occur by activating the pressure receptors through massage. This in turn causes an improved gut motility and improved vagal activity. This enhanced vagal activity causes an improved release of hormones that control food absorption, being insulin-like growth factor I, gastrin and oxytocin. These are two peptide hormones that play a role to an improved weight gain (Lai et al., 2016; Saeadi et al., 2015; Field et al., 2010; Kulkarni et al., 2010; Massaro et al., 2009; Hernandez-Reif et al., 2007; Lee, 2005). It was also found to improve the release of insulin by up to 62% in neonates (Saeadi et al., 2015).

EEG studies that have been conducted on pre-term infants receiving massage have shown a beneficial effect on cerebral function. There was also a relative increase in global EEG spectral power in delta and beta frequencies in massaged infants who received massage as a form of care (Lai et al., 2016). Massage has a positive effect on cognition and this is thought to be through the impact on the autonomic nervous system through the increased secretion of norepinephrine and its effect on attention and memory and the elevation of the infant's arousal level (Feldman and Eidelman, 1998).

Bilirubin levels are decreased in infants receiving massage due to the stimulation of intestinal movement. This causes increased defecation and allows the infant to pass meconium at a faster rate which contains the bilirubin (Basiri-Moghadam et al., 2015). Massage also stimulates the vagus nerve which again increases the frequency of bowel movements and decreases the enterohepatic circulation of bilirubin (Basiri-Moghadam et al., 2015). A third reason for the decreased bilirubin levels is that, massage increases flow of blood, tissue fluids and lymph in the subcutaneous tissues. This causes an increase in the collection and excretion of waste products such as

bilirubin. This study was limited in results due to the small sample size of 59 infants (Basiri-Moghadam et al., 2015).

Stress levels have been shown to decrease by using massage due to lower plasma cortisol levels (Kulkarni et al., 2010). This shows that massage is a non-invasive and cost-effective way of decreasing stress and pain levels in therefore promoting the wellbeing of these infants (Lai et al., 2016; Choi et al., 2015; Cândia et al., 2014; Ardiel and Rankin, 2010; El-Dib et al., 2010; Kulkarni et al., 2010).

Through these mentioned processes we also see that massage can promote improved gastrointestinal function, increase bowel movements and improve regular stool discharge (Choi et al., 2015). There is a significant increase in gastric motility in post massage period. This leads to better absorption of nutrients resulting in better weight gain (Ardiel and Rankin, 2010; Kulkarni et al., 2010).

Massage has also been shown to improve neurodevelopmental outcomes at two years of age (Procianoy et al., 2010; Ho et al., 2010). Premature infants are also deprived of the cutaneous stimulation that occurs normally through the amniotic fluid and uterine walls. This stimulation has been shown to be involved in the neurodevelopment of the infant due to the impact that the sensory system has on normal development. The improvement in neurodevelopment was also attributed to regulating and organising behaviours and stress reduction (Álvarez et al., 2017; Ho et al., 2010). Children who received a therapeutic massage as part of their treatment were shown to have longer periods of alertness and more organised behaviour. This was shown to play a role in the improved neurodevelopment (Ferreira and Bergamasco, 2010). Consensus has not been reached for the appropriate duration of massage sessions but there is consensus that the child's vital signs and body language should be monitored in order to establish the appropriate amount for each specific child (Álvarez et al., 2017; Ferreira and Bergamasco, 2010). Consensus has not been reached regarding the use of a massage medium such as oil (Álvarez et al., 2017; Ferreira and Bergamasco, 2010). Studies have shown where oil-based massage is used versus no massage there is an improvement in weight gain (Kumar et al., 2013). There was no third group showing massage without a medium used to assess the difference between the three

options. In the studies that have been conducted, there have not been any significant results in large studies showing a difference between the use of a massage medium and not using one.

2.15 Joint Compressions and Passive Movements

Premature infants are at risk for developing bone disease and bone fractures due to the limited formation of bone mass in utero and to limited activity. Inactivity is associated with decreased bone mineral density and physical activity promotes bone development (Field et al., 2010). The period of greatest bone mineral formation in utero happens during the last trimester of pregnancy. For this reason, osteopenia is common in VLBW pre-term infants (Litmanovitz et al., 2007). Pre-term, ill infants are also at risk for pressure sores and for this reason also require movement and position changes (August et al., 2014).

The muscular walls of the mother's uterus allow for resistance and weight-bearing experiences as the foetus moves their arms and legs. The mother is also changing positions throughout the day and this causes the movement plane to change, which allows for different mechanical planes to be activated allowing the foetus more movement (Sivert, 2011; Land and Schoenau, 2008). A decrease in function when the foetus is born prematurely into the NICU environment leads to a decrease in osteoblast activity. This creates less osteoid structure to mineralise even if all nutritional needs are being met. This is why physical exercise with joint compressions should be included in the developmental care to re-engage the ossification process (Sivert, 2011) .

The passive flexion and extension of the limbs has been shown to improve bone density and improve bone growth (Diego et al., 2014; Field et al., 2010)Passive movements have been shown to increase serum bone formation markers, namely bone specific alkaline phosphates. These cause increased bone and body mass and prevented bone strength deterioration (Field et al., 2010). There is an improved bone mineralization and skeletal growth associated with daily physical activity in premature infants (Massaro et al., 2009). Passive range of motion exercises of large joints have resulted in increases leptin and insulin-like growth factor (Litmanovitz et al., 2007;

Nemet et al., 2002). This was a study conducted on a sample size of 20 VLBW premature infants. The programme consisted of daily passive range of motion movements with gentle compressions on all limbs five days per week for four weeks. This study was conducted for eight weeks and started during the first week if the infant's life. The mean gestational age was 27.3 weeks (Litmanovitz et al., 2007). Another study compared passive exercises with massage only. This was done on 30 infants ranging between 28 and 32 weeks of gestation. Both groups had an increase in weight gain. Exercise also showed an increase in calorie consumption while massage increased the vagal activity (Diego et al., 2014).

Passive range of motion exercises with gentle compression at the end of range have been shown to cause an increase in joint pressure and muscle tension. This leads to an increased mechanical load on the bone-muscle unit, increased lean muscle mass and change in bone metabolism and mineralization (Diego et al., 2014; Litmanovitz et al., 2007; Eliakim et al., 2002; Moyer-Mileur et al., 1995). Mechanical load is a good stimulation tool for bone formation in children. Evidence is increasing to show how important intrauterine movements are to foetal bone development (Litmanovitz et al., 2007). Mechanical strain on the bones and joints causes the stimulation of bone formation and growth. The osteoblasts increase in activity in response to mechanical strain both in utero and in the NICU (Moyer-Mileur et al., 1995).

During foetal development there needs to be sufficient transfer of calcium and minerals from the placenta to cause appropriate growth and mineralisation of the foetal skeleton. When the umbilical cord is cut, an adjustment in the regulation of mineral homeostasis occurs in the neonatal period. The neonate becomes dependent on the intestinal calcium intake, skeletal calcium stores and renal calcium reabsorption which help to maintain the normal blood calcium during the skeletal growth period (Land and Schoenau, 2008). Postnatally there are important adaptions of the skeletal system to extra uterine conditions that occur. The bone mineral density of the long bones decreases during the first months of life by 30% reportedly due to a rapid increase in bone marrow production. Bone marrow is said to increase faster than the cross-sectional area of the bone. This process is known as physiological osteoporosis of infancy (Land and Schoenau, 2008; Rauch and Schoenau, 2002).

A systematic review was conducted to assess the literature available on whether physical activity improves bone mineralisation in pre-term infants. This study included randomized controlled trials, quasi-experimental trials, meta-analyses, systematic reviews, qualitative studies, and mixed studies. Studies were included if participants were born at <37 weeks gestation and an assessment of bone quality was done. Twelve trials met the inclusion criteria allowing for a sample size of 562 participants. The conclusion of this study showed that a daily physical activity programme of passive movements with joint compressions improved bone mineralization (Stalnaker and Poskey, 2016).

Conversely, a randomized controlled trial of 50 preterm participants received passive movements and joint compressions from one week of age. This study did not find any significant differences in bone mineralization between groups (Shaw et al., 2018).

2.16 Positioning

The musculoskeletal system of the neonate is extremely plastic and for this reason it is very responsive to positioning. Foetal and neonatal movements and postures are vital to the formation of the skull, spinal curvatures and joints in infants (Sweeney and Gutierrez, 2002). During the third trimester in the uterus the ideal flexion position and midline orientation is adopted by the infant. This time is either missed entirely or partly by premature infants depending on the gestational age. The ideal flexion position is that the arms and legs are flexed, and the trunk is tucked forward. Positioning of the infant is facilitated by physiological flexion. This means there is flexion of the shoulders, hips and knees. There is scapular protraction and a posterior pelvic tilt. This position promotes joint alignment, midline orientation and symmetry in a newborn. This in turn aids in neuromuscular development and supports neurodevelopment and promotes self-soothing (Madlinger-Lewis et al., 2014; Zarem et al., 2013; Waitzman, 2007; Sweeney and Gutierrez, 2002). Pre-term infants are also at risk for pressure sore development and this can be added to the reasons requiring positioning (August et al., 2014).

Postural stability is the foundation of all motor milestones and is influenced by gravity and neurosensory input. Premature infants are unable to maintain any postural stability without assistance. For this reason the positioning is very important (Coughlin et al., 2010). There is a maturation-related hypotonia that is found in premature infants. Due to this, the benefit from positional assistance in the semi-flexed and midline postures are important as the flexor tone in a premature infant does not match that of a cramped uterine environment of 40 weeks gestation (Ramachandran and Dutta, 2013; Coughlin et al., 2010). Premature infants lack tonal response and muscle strength at birth and for these reasons often assume extended positions of the neck, back and extremities (Madlinger-Lewis et al., 2014).

Foetal development, as mentioned above, occurs in the amniotic sac. This sac provides the infant with boundaries that allow for the flexed position. The brain is also wired to promote this position and midline alignment. Physiological flexion aids in the development of flexor muscle tone and the stretch reflexes that are present in newborns (Waitzman, 2007). Another reason for positioning is to ensure that there is a risk of these infants developing muscle asymmetry and tightness which in turn could lead to developmental delay (Waitzman, 2007). The excessive hip abduction and external rotation is connected to a shortening of the tensor fascia latae and iliotibial band. This has been linked to an excessive toe-out gait in 62% of pre-term infants between the ages of three and four and a half years of age (Sweeney and Gutierrez, 2002). Developmentally supportive positioning allows the premature infant the postural and proprioceptive support needed to orient themselves in their environment (Coughlin et al., 2010). Positioning in the first few weeks of life is very important to enhance the flexor tone and strength and for that reason allowing the extensor tone to be balanced (Waitzman, 2007).

Premature infants that require endotracheal ventilation are often placed in an excessive cervical lordosis with neck hyperextension. If these postures are left uncorrected they can cause the anterior neck flexor muscles to be weaker which later on in infancy can negatively influence head centring and hand coordination of midline and hand to mouth activities (Sweeney and Gutierrez, 2002). This can contribute to a delay in gross motor milestones.

Nesting has been shown to provide some proprioceptive input as the various nesting positions enhance the contact of the limbs with the rest of the body, and by doing so is said to improve proprioceptive input (Ferrari et al., 2007). There is, however, no document of the amount of proprioceptive input that is adds. In a study conducted on ten healthy pre-term infants, videography was used to observe responses to the use of nesting and no nest being used. This study showed that when the infants were lying in the nest, they adopted a more flexed posture with shoulder adduction, and elbow, hip and knee flexion. Their heads were also frequently in the midline (Ferrari et al., 2007).

In a randomised controlled trial on 19 pre-term infants, it was documented that the prone position showed improved lung function by optimising the breathing pattern (Gouna et al., 2013). This was in contrast to another randomised control trial, also conducted on 19 pre-term infants which showed no difference between prone and supine on respiratory rate, tidal volume or lung compliance (Levy et al., 2006). These studies show varying responses for respiratory function with regards to positioning.

In a randomised, time series with crossover study, 35 pre-term infants were treated with prone and supine positioning techniques to study the gastric residual volume following feeding (Chen et al., 2013). This study documented that prone position for the first 30 minutes post feed, thereafter supine changes were the most efficient for gastric residual volume (Chen et al., 2013) and that a combination of various nesting positions aids in gastric functioning.

Early intervention can be a costly and time-consuming activity. Research has shown that there are various programmes and techniques that can be put into place in a NICU-environment to encourage the best start for these patients. Early intervention does not need to be costly but with the correct techniques can be performed in the under resourced areas of our country for all children. Legislation in South Africa has proposed that early childhood development programmes be implemented across the country from birth to nine years rather that the traditional six years of age (Development, 2009). The majority of the research conducted on early intervention in

South Africa does not include NICUs. There is a major gap in the research in the South African context with regards to early intervention.

2.17 Developmental assessment

Developmental assessments are used to document the range of developmental skills that an infant or child masters during a specific time frame. These standardised tests are used to document current developmental status, monitor changes over time, identify infants and children who are at risk of developmental delay and allow for early intervention (Rademeyer and Jacklin, 2013; Majnemer and Snider, 2005). Standardised tests are psychometric tools designed to measure an individual's developmental status and compare it with would be expected of an individual of the same age. The tests are structured to be conducted in a specific manner and this allows for the standardisation (Rademeyer and Jacklin, 2013).

2.17.1 Bayley Scales of Infant and Toddler Development Third Edition

This test is widely used across the world in both the clinical and research fields of paediatrics. The BSID-III is considered the gold standard of developmental assessments (Rademeyer and Jacklin, 2013). This test is structured in such a way that it allows for comparison between the various components as well as against the norm references (Milne S, 2012). It is a revised version of the BSID-II.

The third revision of the scales produces three composite scores: the Cognitive scale (range 55 – 145), which assesses sensorimotor development, exploration and manipulation, object relatedness, concept formation, memory and simple problem solving; the Language scale (range 45 – 155), which consists of Receptive Communication (verbal comprehension, vocabulary) and Expressive Communication (babbling, gesturing and utterances) subtests; and the Motor scale (range 45– 155), which consists of Fine Motor (grasping, perceptual-motor integration, motor planning and speed) and Gross Motor (sitting, standing, locomotion and balance) subtest. (Picciolini et al., 2015). An abnormal outcome on each sub scale is a score below 70. An at risk score is a score between 70 and 85 (Ballot et al., 2012).

The BSID-III was developed and standardised in 2006 on a sample of 1700 American children aged between one and 42 months. There were equal numbers of males and females in this process. The participants were also matched for parent education level, race and geographic area (Milne S, 2012). The BSID-l was normed on a large sample of South African children (Richter and Griesel, 1988). The validity of the BSID-III was confirmed on a sample of black South African in 2013 (Rademeyer and Jacklin, 2013).

The average reliability coefficients were calculated using Fisher's z transformation. The scale composite average reliability coefficients ranged from .91 for Cognitive, .93 for language, .86 for fine motor and .91 for gross motor. The lowest reliability coefficients were obtained on the younger groups from one to five months (Albers and Grieve, 2007). The BSID-III manual describes a series of validity studies that were conducted. The index score was .60 when compared to the BSID-II (Albers and Grieve, 2007). A reliability study was done between the BSID-III and the Test of Infant Motor Performance (TIMP) using an intra class correlation coefficient (ICC). The ICC for the TIMP was 0.79 and for the BSID-III cognitive scale was 0.73 and for the BSID-III motor scale was 0.75. It was also shown to have high inter-rater reliability between three testers (Manandhar et al., 2016; Campbell et al., 2013).

Researchers have discovered that the BSID-III underestimates the developmental delay in children when compared to the BSID-II (Anderson et al., 2010). It was found that the use of the developmental quotients may allow for full range of the developmental disabilities to be documented. The BSID-III was designed using different statistical tests to the BSID-II and this has been the documented reason for the underestimation of the scores (Duncan et al., 2015; Luttikhuizen dos Santos et al., 2013; Milne S, 2012; Moore et al., 2012b). Despite these findings, the BSID-III is still seen as the best practice tool for diagnosing developmental delay as it provides a comprehensive picture of the child's development. It allows for each area to be separated to allow the appropriate treatment plan to be adapted for each child (Milne S, 2012).

2.17.2 Griffiths Mental Development Scales III

The Griffiths Mental Development Scale III is a measure to assess the mental abilities in infants and young children. It consists of five scales: locomotor; personal-social; hearing and speech; eye and hand; and performance. A total raw score is calculated and converted into a Mental Age Scale Quotient and a General Quotient can be calculated for each scale (Richter et al., 2016). It assesses children between the ages of birth to eight years. It was standardised in the United Kingdom on 426 infants. The test duration is reported at approximately an hour (Luiz et al., 2006). It has been used successfully on the South Africa population in a study investigating the effects of anti-retroviral treatment on HIV positive children's developmental status (Laughton et al., 2018). The construct validity and reliability for the South African population was tested for this scale on a sample size of 430 participants across racial lines. The sample size had an age range of 54 to 83 months (Luiz et al., 2001).

2.17.3 Peabody Developmental Motor Scales

The Peabody Developmental Motor Scales is motor developmental programme that is used to assess the motor abilities in infants and children from birth to five years of age. The program consists of six subtests. The program allows for composite scores in gross motor quotient; fine motor quotient and total motor quotient. The test was standardised on United States infants and children and the administration of the test takes an hour (Tieman et al., 2005). In a study conducted on 48 infants, the construct validity between the BSID-III and the Peabody developmental Motor Scales was assessed. The study found the validity to be supported between the two tests (Connolly BH, 2012).

2.17.4 Test of Infant Motor Performance

The Test of Infant Motor Performance is an assessment tool that can be used from fro infants from 34 weeks gestational age to 17 weeks post-term. The Test of Infant Motor Performance assesses postural and selective control in early infants (Campbell et al., 2013). The validity of this assessment tool has been documented over a variety of population groups and requires approximately 30 minutes to administer (Byrne and Campbell, 2013). Convergent validity between the Test of Motor Performance and the BSID-III was documented. This was tested on 145 pre-

term infants aged between 29 and 34 weeks gestation, who were tested at six weeks corrected age. It reported that the Test of Motor Performance showed better results in the younger population (Campbell et al., 2013).

Developmental assessments for birth and toddlers are well researched. Numerous tools exist which have various strengths and weaknesses. The BSID III was chosen as the assessment tool for this study as it has been used on the South African population with great success (Ballot et al., 2017; Rademeyer and Jacklin, 2013).

2.18 Conclusion

This literature review shows the need for EI to be implemented with premature infants. This at-risk population group shows the risk of developmental delay depending on a number of factors such as birthweight and gestational age. The various intervention strategies that have been mentioned here all have the potential to improve the developmental outcomes in these children. There is a need for further research to be conducted on the efficacy of interventions combined into one programme and the impact on developmental status thereof.

Chapter 3: METHODOLOGY PHASE ONE- PROGRAMME DEVELOPMENT

Research Question

Does an NICU Developmental Programme have an impact on the developmental outcomes of South African pre-term infants?

Objectives

- To develop a NICU developmental programme.
- To establish the developmental status of infants aged 18 months corrected age who received the programme whilst in NICU.
- To establish the developmental status of infants aged 18 months corrected age who did not receive the programme whilst in NICU.
- To compare the two groups in terms of motor, cognitive and language development at corrected gestational age and then at six monthly intervals until they are 18 months old (corrected age).
- To determine whether clinical and demographic data are associated with developmental outcome.

This study consisted of two phases, the programme development and secondly the intervention and follow-up. In this chapter, the methods used to conduct phase one of this research will be discussed.

3.1 Study design

This phase of the study was conducted using a modified version of the nominal group technique (McMillan et al., 2016; Potter M, 2004).

3.2 Ethical Considerations:

Prior to the study commencing, ethical clearance was obtained from the Committee for Research on Human Subjects (Medical) of the University of the Witwatersrand (Clearance certificate number M120817- See Appendix I).

3.3 Study Population:

A total of 10 experts in the fields of paediatric neonatology, paediatric neonatal nursing, and paediatric physiotherapy were included on a review panel.

3.3.1 Inclusion Criteria:

The following inclusion criteria were used for this section of the study:

- All experts have at least 10 years of experience in both the clinical and research fields of infant development.

3.3.2 Exclusion Criteria

No exclusion criteria were applied for this phase of the study.

3.4 Phase 1 Procedure:

Potential experts were identified in the Johannesburg area. Participants were invited from both private and public sector. Letters of invitation and information was sent to each expert. A suitable date was identified. A total of 10 experts agreed to participate in the review panel and met at the Physiotherapy department at the University of the Witwatersrand. Participants signed informed consent before the discussion began.

The following professions were represented:
2 neonatologists

2 neonatal nurses
1 midwife
1 physiotherapist working in NICU
2 physiotherapists working in the neurodevelopmental field
1 paediatrician
1 occupational therapist

At this review panel the individual components of the programme were explained by the researcher to the experts. The researcher was not a member of the expert panel. The rationale behind the chosen treatment techniques, including massage, passive movements and joint compressions as well as nesting in the developmental programme. Various options were presented to the expert panel. These options included the order and timing of the programme. The researcher explained the clinical points that had been observed in practice prior to the research commencing and explained the reasoning behind the programme to be tested. Time was allowed for discussion and questions regarding the rationale and delivery of the programme were asked. During this discussion session, the experts added their opinions on various treatment techniques that could also be included, and this was discussed. Consensus was considered to have been reached if at least eight out of the ten participants agreed on a point. The point of kangaroo mother care was discussed at length. Consensus was reached not to include this treatment technique in the intervention group. The rationale behind this was that the act of kangaroo mother care is a standard practice but not the age of initiation, duration of each session or the position that the child is held in. For these reasons it was agreed upon to be left out as it would bring confounding variables into the results.

Questions were raised as to what time point would be most appropriate to start the programme. Consensus was reached that the programme should only commence once the infant was no longer receiving any mechanical ventilation. It was decided that therapy could commence once the infant was on oxygen therapy.
The question of the use of a massage medium such as oils was also discussed. It was agreed unanimously that no medium would be used. This was to ensure that the effect was from the massage and not the medium.

The point regarding the standard of care was discussed. The literature states many techniques such as Kangaroo mother care, clustering care and nesting. Unfortunately, in the South African NICU context there is no standard across either private or public hospital settings. This could be due to facilities being under-resourced as well as lack of training in the latest evidence-based research that should be guiding best practice.

Duration and frequency of treatment were discussed, and consensus was reached. It was decided that that programme would be done once daily whilst the child was admitted. It would be no longer than 15 minutes per child to ensure no over-stimulation of the infant was experienced. The programme would be performed while the infant was in a quiet alert state. Standard positioning changes were performed between the daily visits by the nursing staff and were documented in the child's file as procedure states.

The use of the BSID III as the primary outcome measure of developmental status of the infants was also discussed. The experts agreed that it was the gold standard to be used in this type of follow-up. It was decided that the frequency of the follow-ups should be done at six, 12 and 18 months corrected age.

Input was also obtained on what demographic and clinical information needed to be included on a data collection form.

Due to the small expert field available in the treatment of pre-term infants this modified nominal group technique was chosen.

3.5 Intervention Programme

The treatment programme agreed upon by the panel of experts is presented below:

3.5.1 Passive movements

The passive movements should be performed from the distal to the proximal joints of both upper and lower limbs (Vignochi et al., 2008). The sequence to be followed is right arm, left arm, right leg, left leg. Limbs should be held with a gentle lumbrical grip and the joint above and below the joint being moved should be stabilised. Each

movement must be performed slowly and rhythmically through available range, ten times on the following joints:

The ankle joint movement consists of planter flexion and dorsiflexion movements.

The knee joint movement consist of flexion and extension.

The hip joint movement consists of flexion, extension, abduction, adduction, lateral rotation and medial rotation.

The wrist joint movements consist of flexion, extension, abduction and adduction.

The elbow joint movements consist of flexion and extension.

The shoulder joint movements consist of flexion, extension, abduction, adduction, medial rotation and lateral rotation.

(Moyer-Mileur et al., 1995; Vignochi et al., 2008).

3.5.2 Joint approximation

The joint approximations are done for both the upper and lower limbs. Limbs should be held with a gentle lumbrical grip. Joint approximations should be done five times on each side. Each compression is held for three seconds (Moyer-Mileur et al., 1995; Vignochi et al., 2008).

For the lower limbs, joint approximations are done by holding the hand over the knee joint to keep the knee extended. The pressure is passed through the ankle, knee and hip in the direction of the hip joint. The hip is flexed to 90° with the knee in extension and the ankle in neutral.

With regards to the upper limb, the researcher places her hand over the elbow to maintain the elbow in extension. The pressure is passed through the wrist, elbow and shoulder in the direction of the shoulder. The shoulder is in 90° flexion with the elbow extended and the wrist in neutral.

(Moyer-Mileur et al., 1995; Vignochi et al., 2008).

3.5.3 Massage

The massage is then performed. This is done from the toes up to the head. The researcher's thumb and fingers are used. Each area is massaged from the distal appendage to the proximal six times (Moyer-Mileur et al., 2013).

Each individual toe is massaged in a circular movement. The foot, ankle and leg then follow. Extra attention must be given to the iliotibial bands (ITB) bilaterally. The iliotibial bands are massaged in the same circular manage motion. This is done to ensure no ITB shortening due to positioning occurs (Sweeney and Gutierrez, 2002).

The abdomen is massaged using the three middle fingers in a clockwise, circular motion.

The thoracic region is massaged using circular movements.

The upper limbs are then massaged. The programme begins at the fingers and moves up to the wrist and through to the shoulder. Again, a circular friction motion is used.

The facial area is also massaged in the same circular friction motion. This is started with the forehead and around the eyes. Then the cheeks are massaged in the same circular motion. Lastly, the chin is massaged

The child is then turned into the prone position and massaged from the lumbar region up towards the head. This is done in circular movements on either side of the spine (Lee, 2005; Moyer-Mileur et al., 2013).

3.5.4 Positioning

The child is then placed in a nesting position to encourage flexion. This is done in the supine position. The supine position was chosen due to the musculoskeletal implications of a flattened skull that has a greater chance of occurring in the prone position due to the head being rotated. This position also allows for preferable vital monitoring by the nursing staff (Picheansathian and Patcharee, 2005). The infant's head must be supported in the midline. The infant is positioned in the midline. Hip and

knee flexion are encouraged by placing rolls of blankets underneath the infant's knees and against the lateral thighs to prevent excessive hip abduction and external rotation.

The shoulders are supported in a slightly forward position to prevent shoulder retraction and allow the hands to the chest. This is done by using rolled blankets and gel packs (Sweeney and Gutierrez, 2002).

The child's vital signs must be monitored throughout the programme to ensure no stress is being experienced. The vital signs monitored should include heart rate, respiratory rate, oxygen saturation and blood pressure. Treatment must be stopped if any of the following were noted:

- heart rate over 180 beats per minute,
- respiratory rate of over 60 breathes per minute and
- systolic blood pressure of over 70mmHg (Davies JH, 2007).(Davies JH, 2007).

3.6 Conclusion

A modified nominal group technique was conducted with a team of experts to agree on the components to be included in an NICU programme. Consensus was reached, and the programme agreed on was ready for further testing. The process for testing this intervention is described in the following chapter.

Chapter 4: METHODOLOGY PHASE TWO- IMPLEMENTATION AND FOLLOW-UP

In this chapter the methodology used to test the newly developed programme.

4.1 Location

The study was conducted at two hospitals with similar NICUs in Gauteng. The standard operating procedures documented at both NICUs confirmed that the two units followed similar operating procedures. The programme was implemented in one of the hospitals. A neighbouring hospital was used as the control group. This was done as it would not be ethical to provide the programme for only some of the infants in a unit. The two hospital were chosen as they are similar with regards to demographics, geographical location and socioeconomic status. NICU wards have multiple beds so, there would also be no guarantee that the mothers in the control group would not start doing massage of their infants as they would see it being done for the infants in the experimental group.

The follow-up assessments were all conducted at a paediatric physiotherapist's practice in Krugersdorp. This allowed the participants to be seen in a practice close to their own homes to minimise travelling distances.

4.2 Unit Protocols

The first unit is the unit where the intervention occurred. This is a ten-bed unit. It has three isolation rooms. There are two paediatricians at this unit. The nursing staff nurses on a one-to-one principle for ventilated patients and one-to-two for non-ventilated patients. Developmental physiotherapy is a standard practice in this unit for all pre-term infants. Speech therapy is used when the paediatricians and nursing staff feel it is required. Visiting policy allows for the parents to be present throughout the day with the exception of ward rounds. Grandparents are allowed for ten minutes on the day of birth. In this unit standard care involves nesting and regular turning;

kangaroo mother care- there is however no standard implementation procedure on this technique and the use thereof is not standard; light adjustment at certain times of the day; developmental physiotherapy and clustering of care.

The second unit is where the control group was sourced from. This is a ten-bed unit with two isolation rooms. There are three paediatricians at this unit. The nursing staff nurses on a one-to-one principle for ventilated patients and one-to-two for non-ventilated patients. Speech therapy is used when the paediatricians and nursing staff feel it is required. Visiting policy allows for the parents throughout the day with the exception of ward rounds. Grandparents are allowed for ten minutes on the day of birth and then every Sunday for an hour. In this unit standard care involves regular position changes; kangaroo mother care- there is however no standard implementation procedure for this technique and the use thereof is not standard; light adjustment at certain times of the day; and clustering of care.

4.3 Ethical Considerations

Prior to the intervention commencing, ethical clearance was obtained from the Committee for Research on Human Subjects (Medical) of the University of the Witwatersrand (Clearance certificate number M120817- See Appendix I).

Permission from the hospitals and the heads of the units was obtained prior to commencement. Informed consent was obtained from potential participant's mother or father on the day of admission. The consent was obtained by the researcher and a nursing staff member. The consent process was free from coercion. This was monitored by the nursing staff member. The registered parents of the potential participants at the hospital were deemed to have the parental capacity for decision-making. The principles of the 2008 Declaration of Helsinki were adhered to. Participants had the right to withdraw at any stage of study with no prejudice (See

Appendix II- Informed consent). This is how the autonomy of the participants was respected.

The control group from unit 2 still received the same care as what they would always have received. No standard treatment was withheld from the participants showing that the beneficence and non-maleficence principles were respected. The principle of justice is a limitation in the study as the study participants were recruited from private facilities. Despite the fact that all racial groups from South Africa were represented, it does not allow for fair treatment to all socioeconomic group of South Africa.

The participants were reimbursed for their travel expenses for the follow up assessments. The follow up assessments were conducted free of charge to the participants.

All data was anonymized and stored in a locked cupboard. All electronic data was stored on an external hard drive in the same locked cupboard. Only the researcher has access to this information.

4.4 Study Design

This phase of the study was an unmatched case-controlled study.

4.5 Sample Selection

The data for 140 infants was obtained. Seventy of these infants were in the intervention group and received the developmental programme and follow up assessments at six, 12 and 18 months corrected age. The 70 infants who were in the control group received standard care but did not receive the intervention, their demographic and clinical data was recorded, and they were followed-up for the assessments at six, 12

and 18 months. It was decided to separate the groups to ensure that parents did not feel their children were not receiving the optimal care whilst in the NICU.

The control and intervention groups were from two different NICU units. These units both collaborate with the Vermont Oxford Network. This tool allows for the development of a research base on best practice in NICUs worldwide to be established. This is a non-profit organisation using clinical audit tools for NICU (Horbar, 1999).

4.5.1 Inclusion Criteria

The following inclusion criteria were used for this study:

- Infants who were born prematurely and admitted to either one of the NICU units of the two chosen private hospitals.
- All infants less than 37 weeks gestational age.

4.5.2 Exclusion Criteria

The following exclusion criteria were used for this study:

- Infants who were transferred to a different unit prior to their discharge from the NICU.
- Infants still on ventilatory support including continuous positive airway pressure (CPAP).

4.6 Sample size

Using the Bayley Scales of Infant and Toddler development III as the primary outcome measure, the sample size of 70 subjects in each group has a 90% power to detect an effect size of 10 with a standard deviation of 15 at the 0.05 level of significance. This

includes a drop-out factor of 15% and a non-compliance of 10%. The effect size of 10 was the same for each developmental area and was based on clinical experience of the researcher and supervisors as well as previous South African studies which used the BSID-lll successfully (Ballot et al., 2017; Rademeyer and Jacklin, 2013; Potterton et al., 2010).

4.7 Assessment Tool

4.7.1 Bayley Scales of Infant and Toddler Development III

The Bayley Scales of Infant and Toddler Development III was chosen as the primary outcome measure for this study as it is able to assess all facets of development and is considered to be the gold standard of developmental assessment (Vincer et al., 2005). The BSID III is a revised version of the Bayley-II. The BSID III does not have a single composite developmental outcome. There are three separate subscales- cognitive, language and motor. The motor scale is further divided into fine and gross motor. The language scale is further divided into receptive and expressive communication. An abnormal outcome on each sub scale is a score <70. At risk scores are considered between 70 and 85 (Ballot et al., 2012). This assessment tool was discussed in detail in the literature review. Table 4.1 details the BSID III composite scores.

Table 4.1 BSID III Qualitative Descriptions of Composite Score Classification

Composite	Classification
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 composite scores give an indication of the child's developmental abilities in relation to the average score. They are based on the sum of the subtests (Bayley, 2006). The composite scores range between 40 and 160. There is a mean of 100 and a standard deviation of 15 (Bayley, 2006).

Table 4.2 BSID III Scaled scores in relation to the Composite scores

Composite Score	Scaled score
55	1
60	2
65	3
70	4
75	5
80	6
85	7
90	8
95	9
100	10
105	11
110	12
115	13
120	14
125	15
130	16
135	17
140	18
145	19

The scaled scores demonstrate a child's performance on a subtest relative to his or her age peers. The scaled scores are calculated form the total raw scores on each subtest and are scaled with a range of 1 to 19, a mean of 10 and a standard deviation of 3.

The BSID III composite and scaled scores allow for the most accurate description of the participants' developmental status.

4.8 Phase 2 Procedure

Training of the researcher and the research assistant in the use of the BSID III was done by the University of the Witwatersrand Physiotherapy Department. Inter-rater testing was done on ten infants prior to the testing starting. Inter-rater reliability was calculated at 100%. The inter-rater reliability testing was conducted on ten subjects of varying ages within the study age range, prior to the study commencing. The subjects chosen had a range of ability spectrums.

The parents of the consecutive infants were approached on the day of admission. The parents were given an information letter regarding the study. They were given an hour to read the information. The researcher then went to each parent and gave them time to ask any questions that they had regarding the study and to discuss any concerns. Only once they had signed informed consent were their babies included into the programme. There was no lower limit to this age. If infants were on mechanical ventilation the programme was only started once they were weaned off. From unit one, six mothers declined to participate. Reasons included distance that they lived from the hospital as well as mothers reporting that they did not think it was necessary. From unit 2, four mothers declined to participate. Their reason included the fact that they wanted the treatment for their children and that their child's doctor didn't tell them about it. This was all done in accordance with the STROBE statement on strengthening reporting in research studies (von Elm et al., 2007).

There was no need for translation of the informed consent sheet as all mothers understood and spoke English.

All relevant medical information was obtained from the hospital records and captured on a data recording form (See Appendix III). Weight, height and head circumferences at birth were included in the information obtained. The group from the one hospital received the intervention programme once they were off ventilator support and the control group received standard NICU treatment. Standard care is any medical care that the infant would require. The only therapy that was done on certain infants was speech therapy if the child required assistance in learning to suck. The nursing care principles are the same in both units.

The programme was delivered in the morning prior to the infant feeding when the child was in an alert-wake state. Before the programme delivery commenced, the information chart was reviewed to ensure there were no health problems that had arisen since the previous session. The vital signs were checked prior to the programme commencing, monitored during the session and then checked once the session had been completed. If children were unstable for any reason the intervention was stopped. This was documented if it occurred. Once the programme had finished, the details were recorded on both the hospital chart and the researcher's notes. The parents were not in attendance for the programme. This was done to ensure that the parents could not do the programme after discharge as this may have had an impact on the outcome of the study.

Once children were discharged from hospital, they were sent a reminder message two weeks prior to the time for their various assessments. They were then assessed using the BSID III in the same physiotherapy practice at corrected gestational age of six, 12 and 18 months of age. All participants had been discharged by the time the six-month assessment was due. The researcher did the intervention in NICU and another physiotherapist who was blinded to which groups the children were in did all the

assessments. The assessor was not aware as to which the group the participant had been assigned to.

The 140 participants who had granted consent were sent reminder messages via text for their six, 12 and 18 month follow-ups. They then contacted the researcher to set up appointment times for their assessments.

The assessments at all three ages were done in the same quiet room on a mat on the floor. The subscales were administered as prescribed in the manual (Bayley, 2006). The cognitive scale was administrated first, followed by the receptive and then expressive communications subscale and then the fine motor and gross motor subscales. The entire test was completed at each assessment time for each child.

Deriving the BSID III scaled scores was done as follows:

- The raw scores from each subtest are calculated
- Table A-1 in the administration manual is then used to convert the raw scores into the scaled scores using the child's age
- The scaled scores are then used to calculate the composite scores to allow for an overall motor, language and cognitive scores to be calculated

The results of the assessment were made available to the parent, and if the child was experiencing significant delays in any area, the appropriate referrals were given immediately. The participant received therapy and was still assessed as per the protocol for this study. No home programmes were given out by the assessor at any stage of any of the assessments.

The information was put into a confidential folder for analysis.

4.9 Statistical Analysis

Data was tested for normality using the Shapiro-Wilk Test. Demographic and clinical data were summarised using descriptive statistics. Continuous variables were tested for consistency within normal distribution via histograms. Transformations were done if not normally distributed. Categorical variables were used in appropriate tests. T-tests were used for independent variables.

The data collected in this study was analysed with the use of STATA. The t test was used to investigate associations between Bayley scores and the intervention programme. The Chi Square test was performed on the Bayley scores as it is categorical data and discrete variables. A 95% confidence interval was used to show relationships and trends. A clinical outcome of BSID III scores of four or greater were used in line with a study conducted using the BSID III on an 18 month group of cardiac surgery patients (Mackie et al., 2015)

A linear regression analysis was done to determine which factors were the best predictors of the BSID III scores at each visit as well as which factors are predictive of change in these scores over time. A backwards model was used to build the regression model. During the model building, any variables that did not significantly improve the results were dropped. Spearman's rho tests were used to measure the strength of association between variables.

The results of this study will be presented in chapter five.

Chapter 5: RESULTS

In chapter five the results of the study will be presented. The data from 140 subjects was analysed. The drop-out rate was low at 7,8%. A pragmatic approach was followed, and all available data was analysed at each time point. The loss to follow-up is presented in figure 5.1.

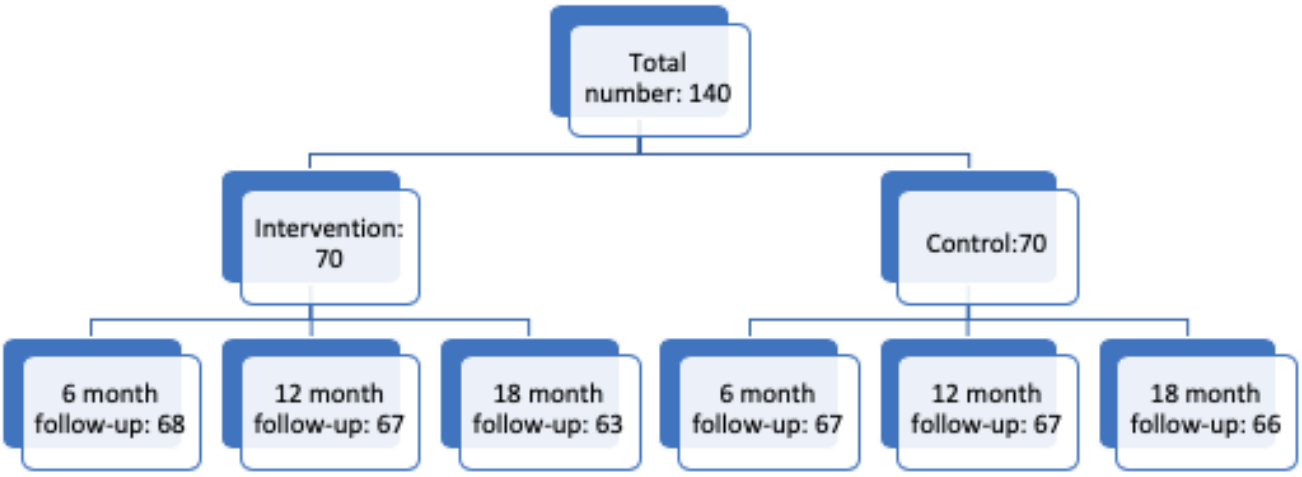


Figure 5.1 Research flow chart

Figure 5.1 explains the study population numbers in each group throughout the study phases. Drop-out was due to three deaths and the remainder of the infants lost to follow up did not arrive for their follow-ups assessments despite receiving reminders. The two infants in the control group and one in the intervention group died. The deaths occurred at corrected ages four, five and seven months. The causes of death were dehydration, motor vehicle accident and the last cause was unknown.

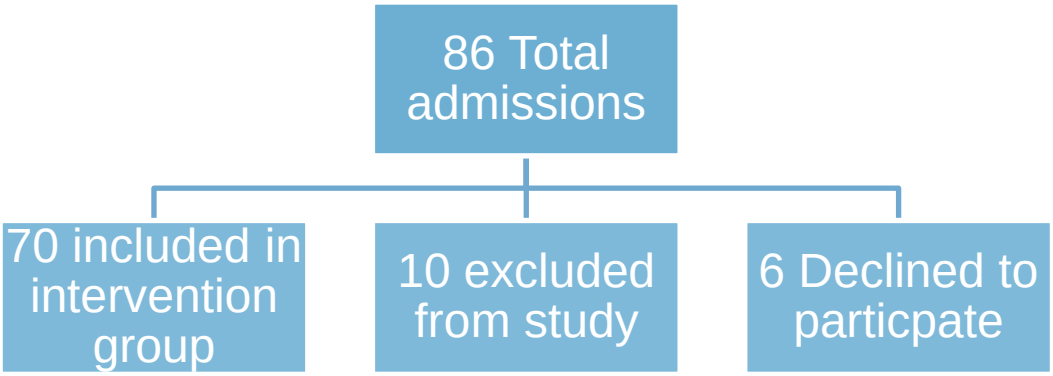


Figure 5.2 Unit 1 Participant Information

Figure 5.2 explains the number of subjects who were approached during the recruitment for the study from Unit 1 which was the intervention site.

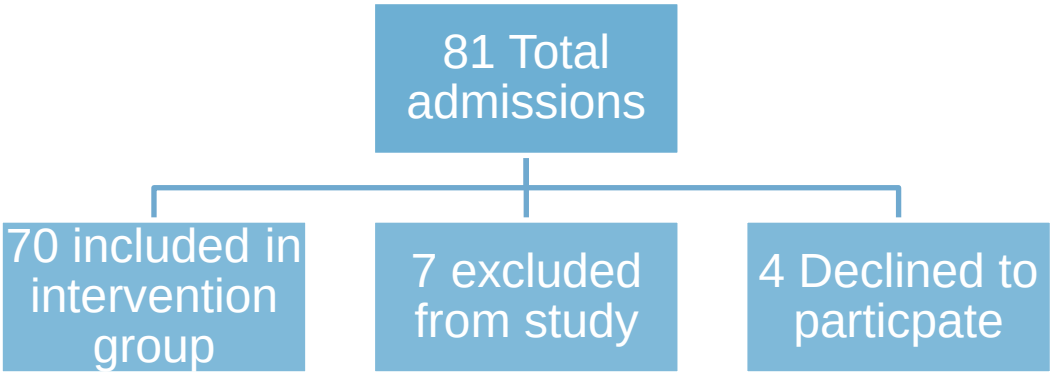


Figure 5.3 Unit 2 Participant Information

Figure 5.3 explains the number of subjects who were approached from the study from Unit 2 which was the control site.

5.1 Demographics

The two groups were well matched for demographic characteristics with no significant differences found between them. The demographic details of both the experimental and the control group are summarised in Table 5.1.

Table 5. 1: Demographics Details

	Experimental group (n=70)	Control group (n= 70)	P-value
Gestational age (weeks) median	32.80 ± 2.6	32.50 ± 2.80	0.53
Birth weight (gr) median	1785.00 ± 560.78	1845.00 ± 571.87	0.89
Birth length (cm) mean	40.30 ± 9.80	40.98 ± 4.10	0.44
Head Circumference (cm) mean	30.60 ± 11.50	30.26 ± 8.90	0.50
Multiple Birth n(%)	15 (21.40%)	18 (25.70%)	0.70
Caesarean section delivery n(%)	69 (98.60%)	69 (98.60%)	1.00
Normal vaginal delivery n(%)	1 (1.40%)	1 (1.40%)	1.00
Males n(%)	38 (54.20%)	35 (50%)	0.61
Females n(%)	32 (45.70%)	35 (50%)	0.61
Total days in NICU	21.00 (± 20.73)	24.50 (±22.13)	0.17

Data is presented as means and standard deviations or frequencies. The mean gestational age in the experimental group was 32.80 weeks (± 2.6) compared to the control group of 32.50 weeks ± 2.8. The mean birth weight of the experimental and control groups were 1785.00gr (± 560.78) and 1845.00gr (± 580.06) respectively. Gestational age determination was done by the nursing staff as per the unit protocol. Both units use the New Ballard Score. This score is an expanded version of the Ballard Maturational score that now includes extremely pre-term infants. The New Ballard Score has been shown to be an accurate and valid gestational age assessment tool (Salandy et al., 2019; Ballard et al., 1991).

There was only one normal vaginal delivery in each group. The gestational age that this occurred was 35 weeks for the experimental group and 32 weeks for the control group. Unfortunately, reasons for caesarean section birth were not documented.

5.2 NICU Details

The following tables describe the various medical treatments and complications that are relevant to prematurity. Table 5.2 describes the surfactant and antenatal steroid use of the participants.

Table 5.2 Surfactant and Antenatal Steroid Use

	Experimental group (n=70)	Control group (n=70)	P-value
Surfactant received n(%)	43 (61.40%)	50 (71.40%)	0.10
Antenatal steroids n(%)	27 (21.40%)	20 (62.80%)	<0.001*

Surfactant received is relatively equal in percentage between the two groups whereas the use antenatal steroids was significantly different with a greater number of infants in the control group having been exposed to antenatal steroids.

Table 5.3 is a summary of the various ventilation types that were used with this group of infants.

Table 5.3 Ventilation details

	Experimental group (n=70)	Control group (n=70)	P-value
Biphasic positive airway pressure (BiPAP) n(%)	21 (30%)	33 (47%)	0.01*
CPAP n(%)	33 (47%)	44 (63%)	0.60
Synchronised intermittent mandatory ventilation (SIMV) n(%)	2 (3%)	4 (6%)	0.40
Time-cycled pressure-limited (TCPL) n(%)	4 (5,71%)	3 (4,29%)	0.70
Oscillation n(%)	1 (1.43%)	0 (0%)	0.30
Oxygen Therapy n(%)	63.7 (91%)	30 (43%)	<0.001*
Total days on ventilation median(range)	1 (0 - 22)	2 (0 - 42%)	0.01*

There was a large difference between the groups with regards to oxygen therapy showing a p value of <0. 001. The control group had a lower frequency of oxygen therapy, but higher percentage of CPAP used. The remainder of the ventilator choices showed no significant differences between the two groups. The total days on ventilation also showed a significant difference with the control group being ventilated longer (p=0.01). The total days on ventilation amount included all forms of ventilation except oxygen therapy. The experimental group spent an average of one day on a

ventilator versus the control group of two days on a ventilator. The numbers in Table 5.3 show total number of participants who received each ventilation type including being weaned from one type to another.

Table 5.4 details the complications of prematurity that were documented between the groups.

Table 5.4 Complications of Prematurity

	Experimental group (n=70)	Control group (n=70)	P-value
IVH n(%)	0	3 (4.30%)	0.08
PVL n(%)	0	2 (2.80%)	0.15
ROP n(%)	0	0	0
Sepsis n(%)	4 (5.70%)	4 (5.70%)	1
Blood transfusions n(%)	5 (7.10%)	5 (7.10%)	1
NEC n(%)	6 (8.60%)	3 (4.30%)	<0.001*
UV Therapy n(%)	38 (54.30%)	45 (64.30%)	0.23

The only complication that showed significance was NEC. There was a difference in the NEC rate between the control and experimental group with the experimental group having a higher frequency. Most other markers were very similar between the two groups.

Table 5.5 shows the differences in the type of feed used for the groups.

Table 5.5 Feed type

	Experimental group (n=70)	Control group (n=70)	P-value
Formula feed n(%)	61 (87.10%)	43 (61.40%)	0.001*
Breast milk n(%)	9 (12.90%)	27 (38.60%)	0.001*

The type of feed given was significantly different between the two groups (p= 0.001). The control group used less formula as compared to the experimental group. The other type of feed was expressed breast milk. Unfortunately, no data could be obtained as to whether the breastmilk was in an expressed form or from breastfeeding directly.

5.3 Developmental Outcome

This section will document the results of the BSID III tests that were carried out on the subjects. The tests were done at six, 12 and 18 months by the same research assistant who was blinded to whether the infant was in the experimental or control group.

5.3.1 Six Month scores

The six-month composite scores for the three developmental areas are described in Table 5.6.

Table 5.6 Composite cognitive, language, motor scores at six months

Developmental facet	Experimental Group (n=68)	Control Group (n=67)	P-Value
Cognitive	98.60 ± 4.80	92.39 ± 5.86	<0.001*
Language	102.30. ± 6.49	98.40 ± 7.12	0.90
Motor	102.26 ± 8.62	88.22 ± 9.84	<0.001*

There were significant differences in both cognitive and motor composite scores both having p values of p<0.001 when tested with a student t-test. The six months scores for the language component do not show any significant difference between the two groups.

Scaled scores are presented in table 5.7.

Table 5.7 Scaled cognitive, language, motor scores at six months

Developmental facet	Experimental group (n=68)	Control Group (n=67)	P-Value
Cognitive	9.70 ± 0.95	8.50 ± 0.96	<0.01*
Expressive language	9.80 ± 1.24	9.60 ± 0.82	0.31
Receptive language	10.80 ± 1.24	9.90 ± 1.59	<0.01*
Fine motor	10.73 ± 1.80	10.10 ± 1.93	<0.01*
Gross motor	8.55 ± 1.76	7.80 ± 2.20	<0.01*

Table 5.7 depicts the scaled scores at six months between the control and experimental groups. This table shows how the experimental group performed better in this area at the six-month age. The scaled score for the cognitive area for the experimental group was 9.7 versus 8.5 for the control group showing a significant p-value of $p<0.0001$.

The scaled scores for language confirm that the experimental group performed better in this area at the six-month age. The expressive language scaled scores of 9.6 for the control group and 9.8 for the experimental group, were not significantly different ($p=0.31$). The receptive language area for the six-month age group showed results of 9.9 for the control group and 10.8 for the experimental group, showing a significant p-value of $p=0.01$.

Fine motor scaled scores showed results of 8.55 for the control group and 10.73 for the experimental group. This result showed a significant p-value of $p<0.0001$. The gross motor area showed the control group having a scaled score of 7.8 and the experimental group 10.1. This was again a significant p-value of $p<0.0001$.

5.3.2 Twelve Months Scores

Table 5.8 shows the BSID III composite scores for the two groups at 12 months corrected age.

Table 5.8: Composite cognitive, language motor scores at 12 months

Developmental facets	Experimental Group Mean ±SD (n=67)	Control Group Mean ±SD (n=67)	P-Value
Cognitive	99.70 ± 4.42	97.61 ± 5.93	0.22
Language	98.60 ± 5.14	95.20 ± 5.10	<0.001*
Motor	102.79 ± 5.54	92.66 ± 8.78	<0.001*

These results show how both the language and the motor sections showed significant p values of <0.001.

Table 5.9 depicts the BSID III scaled scores at 12 months between the control and experimental groups.

Table 5.9 Scaled cognitive, language, motor scores at 12 months

Developmental facet	Experimental group (n=67)	Control Group (n=67)	P-Value
Cognitive	9.90 ± 0.88	9.50 ±1.19	<0.02*
Expressive language	10.20 ± 1.37	9.40 ± 0.89	<0.02*
Receptive language	14.20 ± 1.3	13.80 ± 0.93	<0.02*
Fine motor	10.28 ± 0.98	9.00 ± 1.26	<0.01*
Gross motor	10.60 ± 1.37	8.50 ± 1.86	<0.01*

Table 5.9 illustrates the scaled scores at 12 months between the control and experimental group in the cognitive area. This table shows how the experimental group performed better in this area at the 12-month age. The scaled score for the cognitive area for the experimental group was 9.9 versus 9.5 for the control group showing a significant p-value of p=0.02.

The expressive language scaled scores of 9.4 for the control group and 10.2 for the experimental group, showed a significant p-value of p=0.0002. The receptive language

area for the 12-month age group showed results of 13.8 for the control group and 14.2 for the experimental group, showing a significant p-value of p=0.0231.

Table 5.9 demonstrates the scaled score differences in the two motor areas of development at 12-months. Fine motor scaled scores showed results of 8.55 for the control group and 10.73 for the experimental group. This result showed a significant p-value of p<0.0001. The gross motor area showed the control group having a scaled score of 8.5 and the experimental group 10.6. This was again a significant p-value of p<0.0001.

5.3.3 Eighteen Month Scores

Table 5.10 shows the developmental scores for the two groups at the 18-month testing age.

Table 5.10 Composite cognitive, language motor scores at 18 months

Parametre	Experimental Group Mean ±SD (n=63)	Control Group Mean ±SD (n=66)	P-Value
Cognitive	99.70 ± 4.42	97.61 ± 5.93	0.22
Language	98.60 ± 5.14	95.20 ± 5.10	<0.001*
Motor	102.79 ± 5.54	92.66 ± 8.78	<0.001*

These results show the same as for 12 months. For both language and motor composite scores there are p values of <0.001 showing a significant difference between the two groups.

Table 5.11 shows the scaled developmental scores at 18 months.

Table 5.11 Scaled cognitive, language, motor scores at 18 months

Developmental facet	Experimental group (n=68)	Control Group (n=67)	P-Value
Cognitive	10.20 ± 0.99	9.30 ± 1.83	<0.01*
Expressive language	10.30 ± 1.47	9.60 ± 2.22	<0.04*
Receptive language	10.30 ± 0.88	9.50 ± 1.03	<0.01*
Fine motor	10.44 ± 0.74	8.95 ± 1.23	<0.01*
Gross motor	10.70 ± 1.18	9.00 ± 0.97	<0.01*

Table 5.11 depicts the scaled score differences for the cognitive, expressive and receptive language and fine and gross motor areas at 18 months between the control and experimental groups. This table shows how the experimental group performed better in this area at the 18-month age in the cognitive developmental area. The scaled score for the cognitive area for the experimental group was 10.2 versus 9.3 for the control group showing a significant p-value of p=0.001.

The expressive language scaled scores of 9.6 for the control group and 10.3 for the experimental group, showed a significant p-value of p=0.047. The receptive language area for the 18-month age group showed results of 9.5 for the control group and 10.3 for the experimental group, showing a significant p-value of p<0.0001.

Fine motor scaled scores showed results of 8.95 for the control group and 10.44 for the experimental group. This result showed a significant p-value of p<0.0001. The gross motor area showed the control group having a scaled score of 9.0 and the experimental group 10.7. This was again a significant p-value of p<0.0001.

5.4 Factors Associated with Developmental Outcome at 18 months

A linear regression analysis was performed to estimate the relationship between the 18 month scores for motor, language and cognitive scores and treatment, while adjusting for confounders and effect modifiers such as gestation, sex, interventions and complications. Antenatal steroid use, ventilation type and duration of ventilation

were omitted from the model as they didn't play a significant role in the model. On consultation with the statistician, during the model building process, any variable that did not significantly improve the results were dropped. During the regression model building process, ventilation was correlated with surfactant use so could not be used in the same model and was therefore omitted. The limited adjusted r squared test was used to identify the best model.

5.4.1 Factors Associated with Motor Scores at 18 Months

A linear regression on the normally distributed composite scores for the 18 month motor results was done and is presented in Table 5.12.

Table 5.12 Linear regression of 18 month motor composite scores

Variable	Observation	Skewness	Kurtosis	Chi2	Prob>chi2
Motor 18 months	129	0.31	0.99	1.03	0.60
Language 18 months	129	0.04	0.01	9.66	0.01*
Cognitive 18 months	129	0.02	0.00	38.44	0.00*

The 18 month results were tested for consistency and normal distribution. It was found that the distribution of motor scores at 18 months was normal but neither language nor cognitive were. When tested via the Spearman's rho = -0.7462 and the test of H_0 showed that length of stay and gestation were found to independent variables with a prob>t = 0.0000. The null hypothesis showing that length of stay and gestation were directly proportional to each other.

A Skewness/Kurtosis test for normality was performed on birthweight. This is presented in Table 5.13 below:

Table 5.13 Skewness/Kurtosis test for normality was performed on birthweight

Variable	Observation	Skewness	Kurtosis	Chi2	Prob>chi2
Birthweight	140	0.01	0.02	10.58	0.00*

Following this a Spearman's correlation was done between gestation and birthweight with a result of Spearman's rho=0.7941. The test of H_0 showed that gestation and birthweight are dependent of each other with the Prob>t= 0.0000. For this reason, gestation was chosen again for the regression analysis.

A Skewness/Kurtosis test for normality was performed on birth length. This is presented in Table 5.14 below:

Table 5.14 Skewness/Kurtosis test for normality was performed on birth length

Variable	Observation	Skewness	Kurtosis	Chi2	Prob>chi2
Length	140	0.03	0.78	5.07	0.08

Following this a Spearman's correlation was done between gestation and length with a result of Spearman's rho= 0.7435. The test for H_0 showed that gestation and length were independent of each other with a Prob>t= 0.0000.

We used a linear regression for analysis of the factors associated with the motor scores. The model was significant with an adjusted r-squared of 42.6. Table 5.15 shows the regression analysis done at 18 months on the motor aspect of the study on the whole group.

Table 5.15 Regression analysis on 18 months motor scores

	Coef.	Std.Err.	P>t	t	95% CI
Gestation	1.25	8.55	0.00*	8.22	1.09
Surfactant	1.26	1.48	0.14	-0.64	4.37
Oxygen therapy	1.31	-1.25	0.212	-4.24	0.95
NEC	2.39	1.22	0.23	-1.82	7.63
IVH	3.96	2.07	0.04*	0.34	16.03
PVL	4.25	-0.03	0.97	-8.57	8.28
Surgery	4.96	0.72	0.48	-6.28	13.38
UV Therapy	1.16	0.99	0.33	-1.15	3.43
Study Intervention	8.57	8.42	0.00*	55.24	89.19

As is evident from Table 5.15, treatment, gestation and IVH were significant predicators of motor outcome at 18 months of age.

Predictors of the motor score when no treatment was provided was done with a linear model and was significant and an adjusted r-squared of 23.6. Table 5.16 shows the regression analysis performed on the control group at 18 months on the motor aspect of the study. This analysis was done to see which factors played a role without the effect of the treatment.

Table 5.16 Regression analysis on 18 months motor scores in the control group

	Coef.	Std.Err.	P>t	t	95% CI
Gestation	0.30	2.46	0.02*	0.14	1.33
Surfactant	1.73	1.45	0.15	-0.96	5.99
Oxygen therapy	1.45	-1.07	0.29	-4.46	1.35
NEC	3.54	2.59	0.01*	2.09	16.28
IVH	4.52	0.45	0.66	-7.03	11.07
PVL	4.02	-0.01	0.99	-8.11	8.00
Surgery	6.96	1.51	0.14	-3.41	24.44
UV Therapy	1.54	1.39	0.17	-0.95	5.23

As is seen from Table 5.16, factors associated with the motor scores in the control group at 18 months were length of gestation and NEC.

5.4.2 Factors associated with language scores at 18 months

Figure 5.4 shows a histogram of language scores at 18 months in the intervention group.

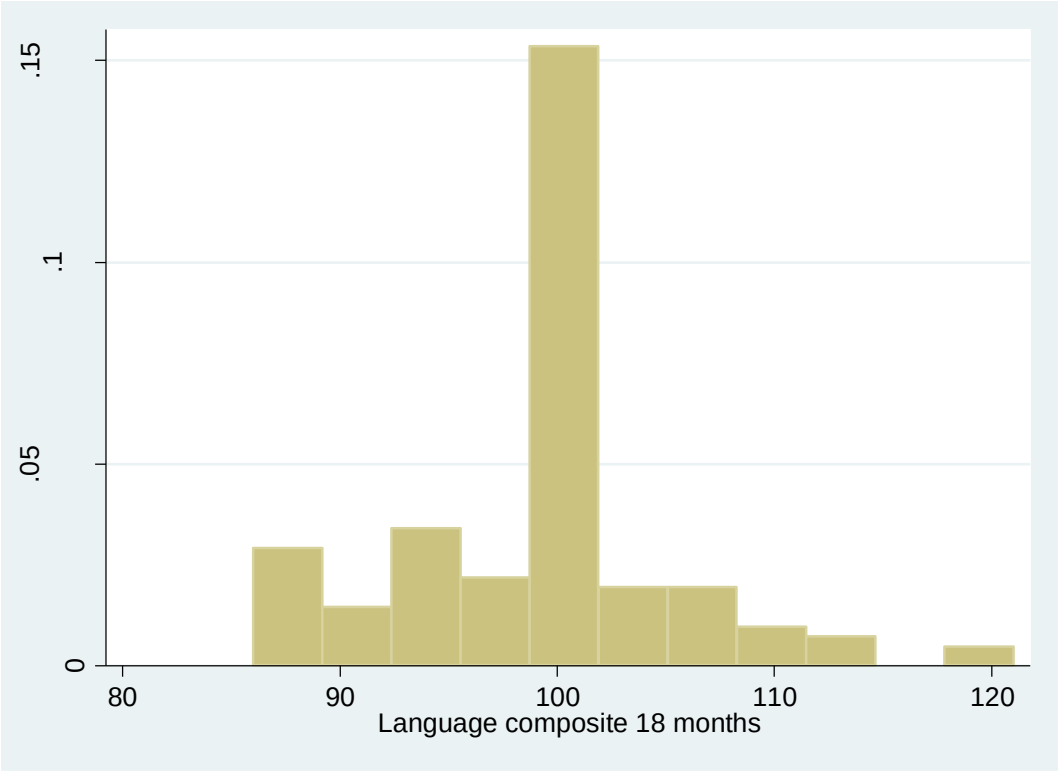


Figure 5.4 Histogram of language scores at 18 months

The histogram is kurtotic, but the linear regression is a robust test and thus was chosen for this analysis. The model was significant with an adjusted r-squared of 22.37.

Table 5.17 shows the results of a linear regression analysis preformed on the 18 month language score data set where the intervention plays a significant role in the outcomes.

Table 5.17 Regression analysis on 18 months language scores

	Coef.	Std.Err.	P>t	t	95% CI
Gestation	0.21	2.36	0.02*	0.08	0.94
Surfactant	2.92	2.58	0.01*	0.68	5.16
Oxygen therapy	1.17	-1.38	0.17	-3.94	0.70
NEC	2.14	-1.35	0.17	-7.12	1.34
IVH	3.55	1.50	0.14	-1.69	12.36
PVL	3.80	-0.28	0.78	-8.58	6.48
Surgery	4.44	0.90	0.37	-4.79	12.79
UV Therapy	1.03	0.77	0.44	-1.25	2.84
Study Intervention	7.67	10.16	0.00*	62.75	93.12

As Table 5.17 shows, the significant factors are that of treatment and surfactant usage.

Table 5.18 shows the regression analysis on the 18 month language scores in the control group to assess which factors affect the outcome.

Table 5.18 Regression analysis on 18 months language scores in the control group

	Coef.	Std.Err.	P>t	t	95% CI
Gestation	0.28	1.50	0.14	-0.14	0.99
Surfactant	1.71	2.15	0.04*	0.26	7.12
Oxygen therapy	1.45	-1.66	0.10	-5.31	0.49
NEC	3.29	0.81	0.42	-3.90	9.27
Surgery	6.53	0.54	0.59	-9.52	16.62
UV Therapy	1.52	1.58	0.12	-0.65	5.45

As shown in Table 5.18, only surfactant use was a significant factor for language scores at 18 months in the control group.

5.4.3 Factors associated with cognitive scores at 18 months

Figure 5.5 shows a histogram of cognitive scores at 18 months in the intervention group.

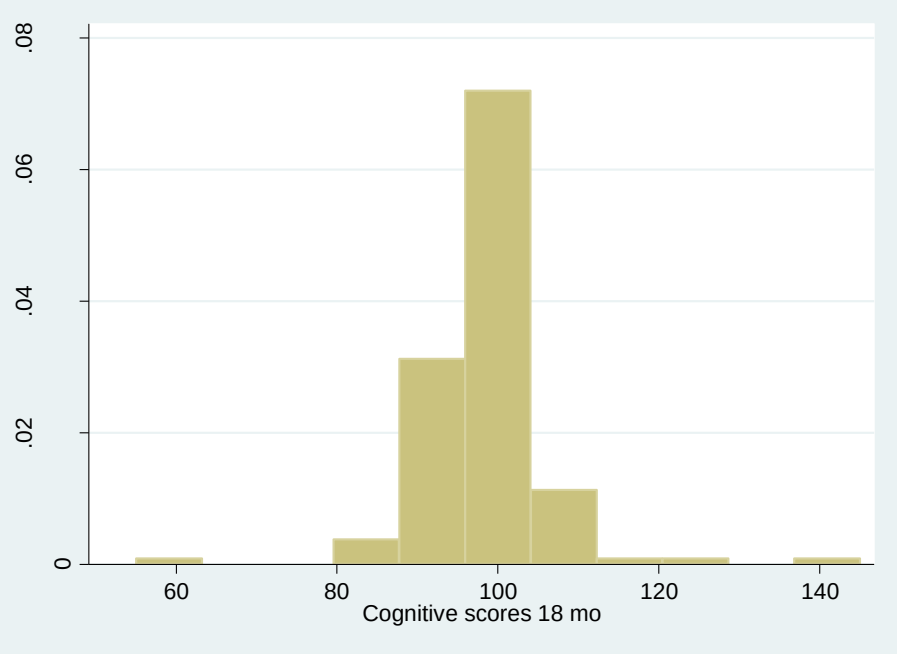


Figure 5.4 Histogram of cognitive scores at 18 months

The data is not normally distributed but approximates it and as the linear regression is robust it was used in this analysis.

Table 5.19 shows the regression analysis performed on the cognitive scores where the treatment was significant.

Table 5.19 Regression analysis on 18 months cognitive scores

	Coef.	Std.Err.	P>t	t	95% CI
Gestation	0.30	2.58	0.01*	0.18	1.37
Surfactant	1.56	3.04	0.00*	1.66	7.85
Oxygen therapy	1.62	-0.94	0.35	-4.73	1.69
NEC	2.95	-0.57	0.57	-7.52	4.17
IVH	4.90	0.97	0.34	-4.97	14.44
PVL	5.26	-0.42	0.68	-12.61	8.22
Surgery	6.14	0.80	0.42	-7.23	17.08
UV Therapy	1.42	0.17	0.87	-2.59	3.07
Study Intervention	10.60	6.45	0.00*	47.41	89.41

Investigation into the factors affecting the results of the were once again, as seen in Table 5.19, treatment, surfactant and length of gestation.

The control group showed a significant model with an adjusted R-square of 9.0.

Table 5.20 shows the regression analysis done on the 18 month cognitive scores on the control group to determine which factors made a difference to the outcomes.

Table 5.20 Regression analysis on 18 months cognitive scores in the control group

	Coef.	Std.Err.	P>t	t	95% CI
Gestation	0.43	2.12	0.04*	0.05	1.77
Surfactant	2.60	2.81	0.01*	2.12	12.53
Surgery	9.33	0.88	0.38	-10.40	26.91

The factors predictive of cognitive function at 18 months were once again shown to be surfactant used and length of gestation.

5.5 Qualitative Description of Cognitive Composite Scores

Composite scores can be qualitatively analysed with regards to the child's developmental level. The scores can be divided into the following categories: Very Superior, Superior, High Average, Average, Low Average, Borderline, Extremely Low (Bayley, 2006). These categories are described in Table 5.21, which documents the qualitative descriptors of the composite scores

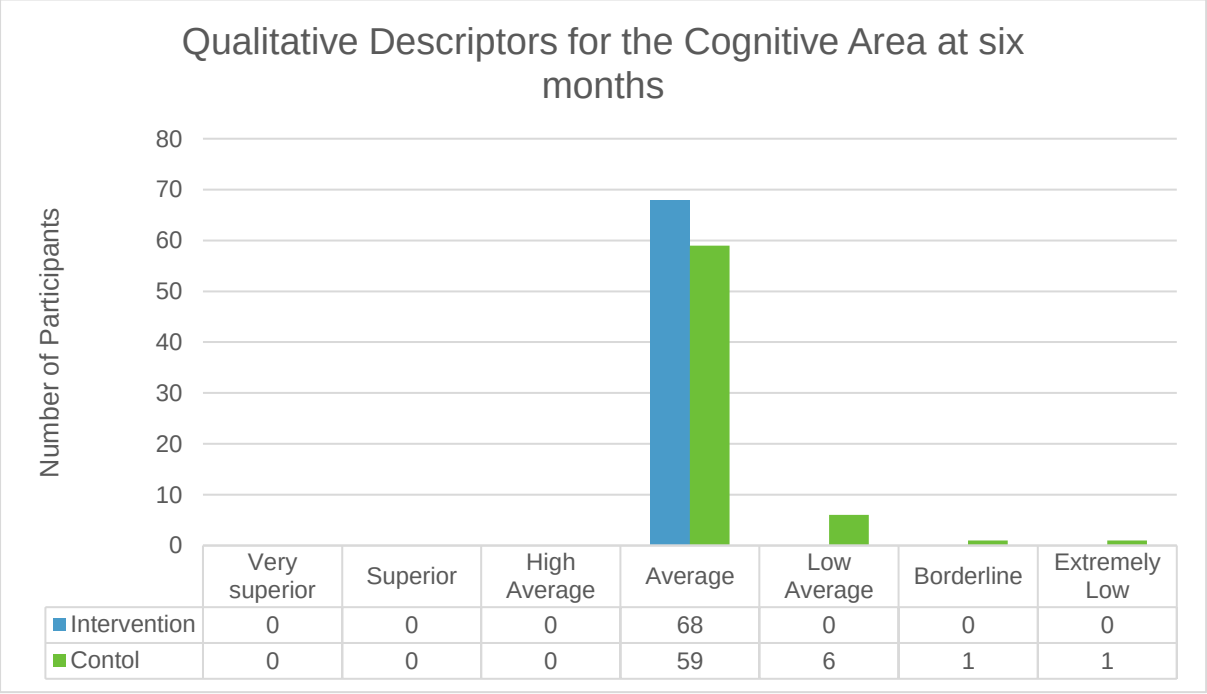
Table 5.21 Qualitative Descriptions for the Composite Scores

Composite Score	Classification
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

In Table 5.21 the descriptors are listed. Children were referred for various therapies depending on the score. If a participant's score fell into the Borderline classification category, they were referred for further therapy.

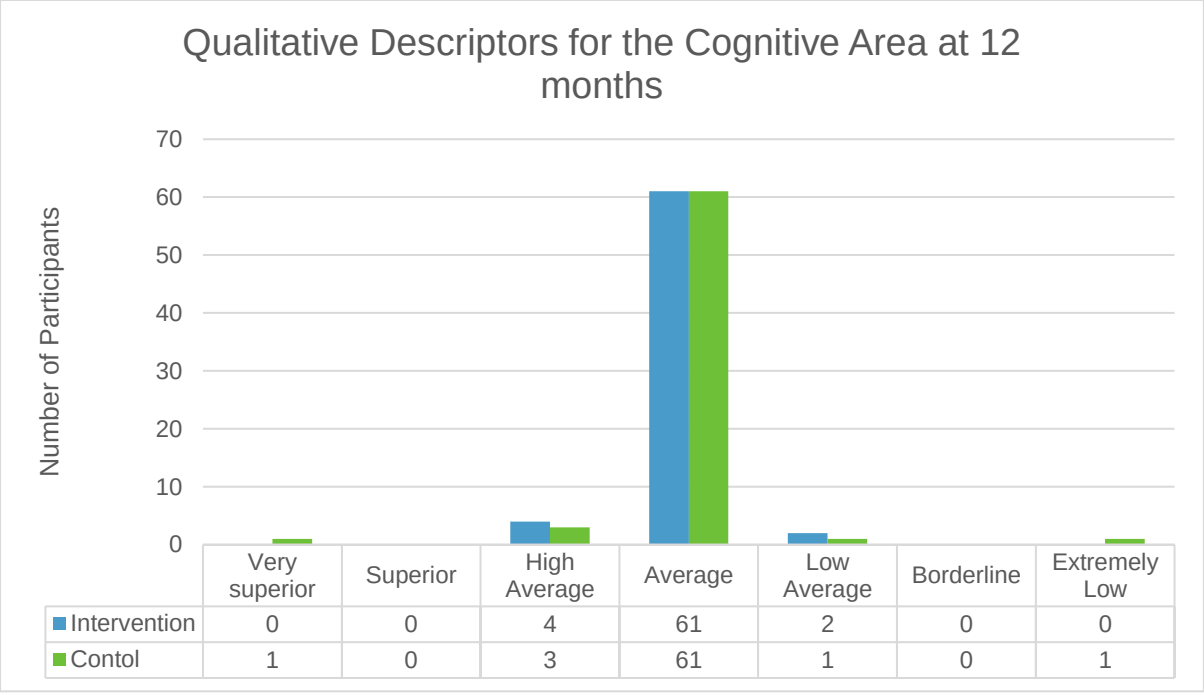
Figures 5.6 – 5.8 document the number of participants falling into each category for the cognitive section at the three testing ages.

Figure 5.6 Qualitative Descriptions for the Cognitive Area at six months



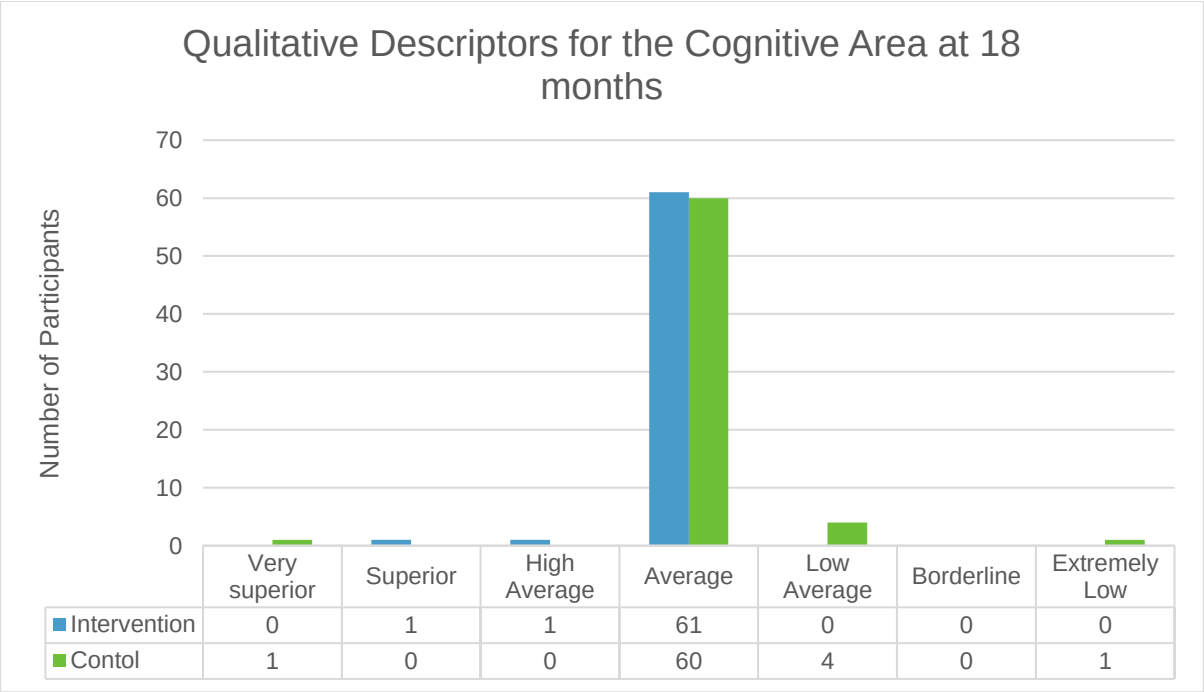
	Very superior	Superior	High Average	Average	Low Average	Borderline	Extremely Low
Intervention	0	0	0	68	0	0	0
Contol	0	0	0	59	6	1	1

Figure 5.7 Qualitative Descriptions for the Cognitive Area at 12 months



	Very superior	Superior	High Average	Average	Low Average	Borderline	Extremely Low
Intervention	0	0	4	61	2	0	0
Contol	1	0	3	61	1	0	1

Figure 5.8 Qualitative Descriptions for the Cognitive Area at 18 months



	Very superior	Superior	High Average	Average	Low Average	Borderline	Extremely Low
Intervention	0	1	1	61	0	0	0
Contol	1	0	0	60	4	0	1

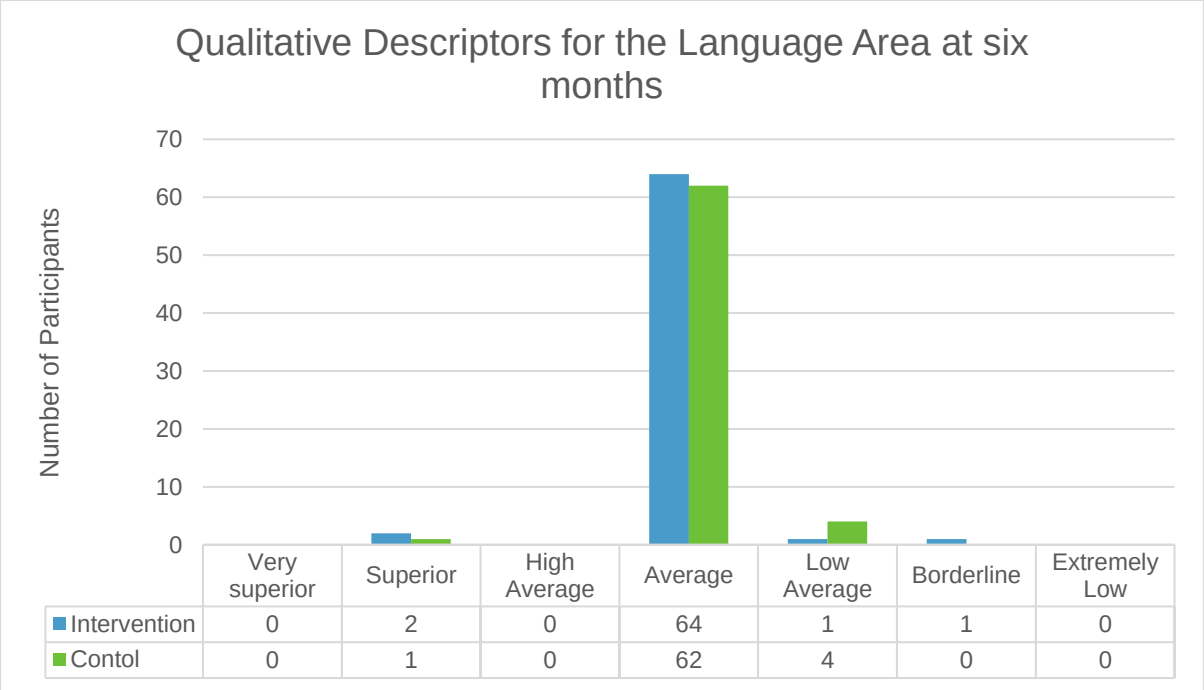
In Figures 5.6 – 5.8 the descriptive statistics show that the control group and the experimental group have very similar results in terms of the developmental levels.

At the six month age two infants were referred for Occupational Therapy (OT). At ages 12 and 18 months there was one infant from each age that was referred for OT.

5.6 Qualitative Description of Language Composite Scores

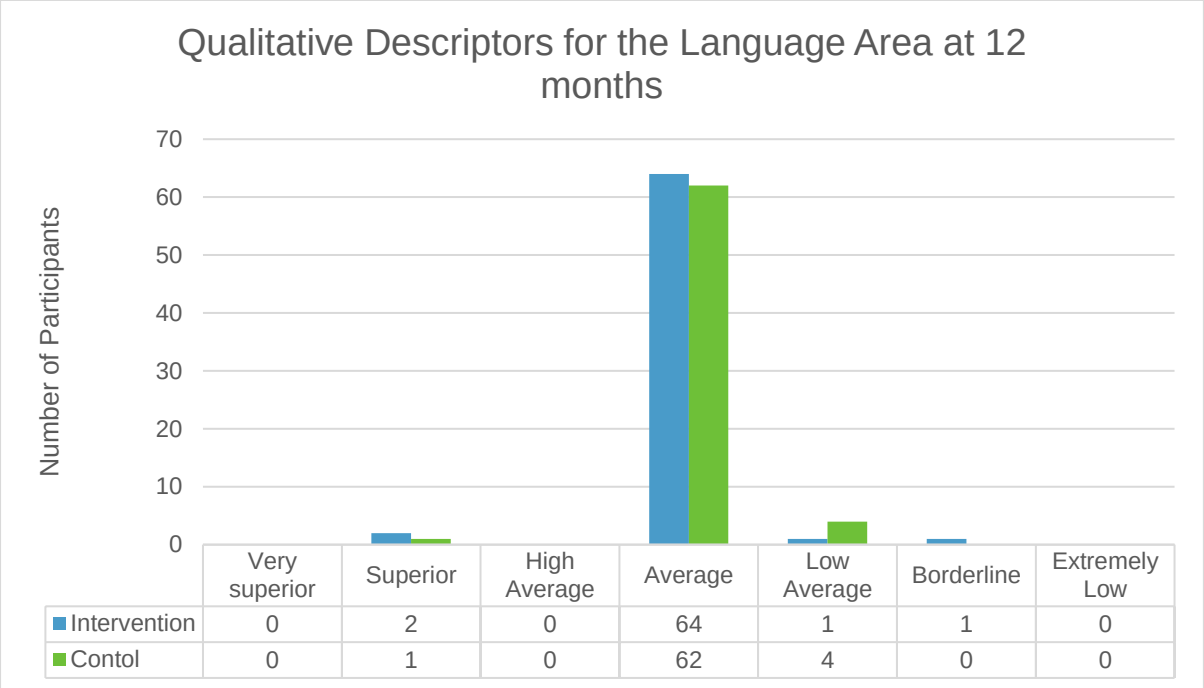
Figures 5.9 – 5.11 documents the number of participants in each category for the language section at all three testing ages.

Figure 5.9 Qualitative Descriptions for the Language Area at six months



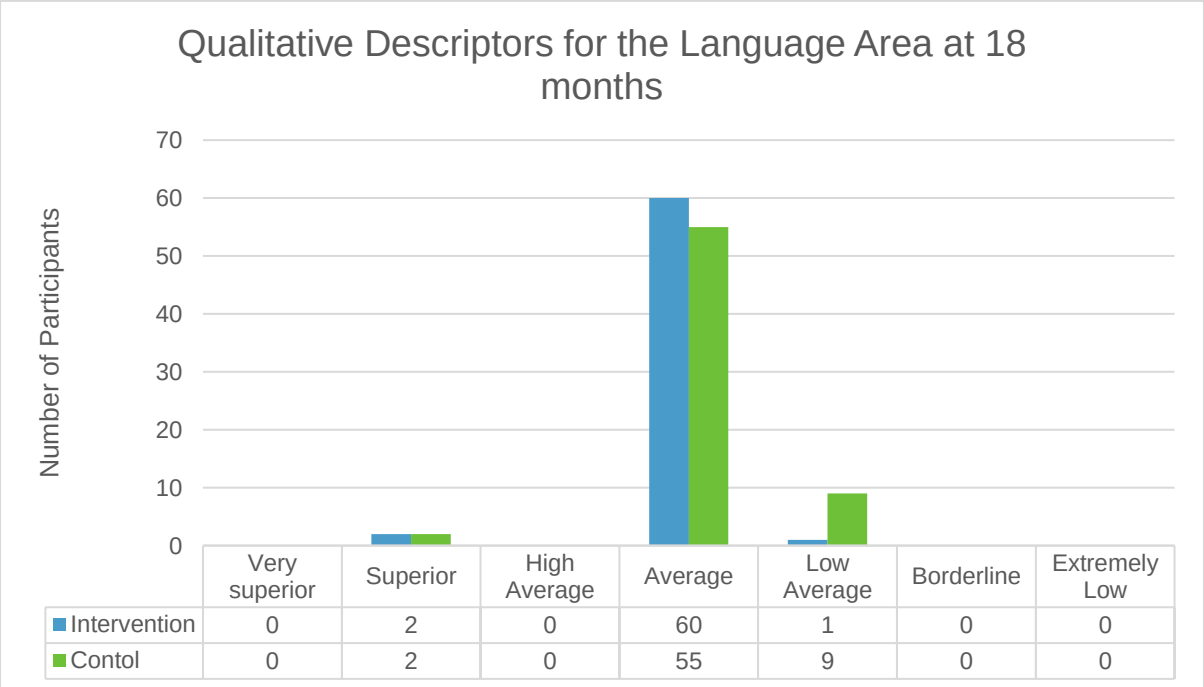
	Very superior	Superior	High Average	Average	Low Average	Borderline	Extremely Low
Intervention	0	2	0	64	1	1	0
Contol	0	1	0	62	4	0	0

Figure 5.10 Qualitative Descriptions for the Language Area at 12 months



	Very superior	Superior	High Average	Average	Low Average	Borderline	Extremely Low
Intervention	0	2	0	64	1	1	0
Contol	0	1	0	62	4	0	0

Figure 5.11 Qualitative Descriptions for the Language Area at 18 months



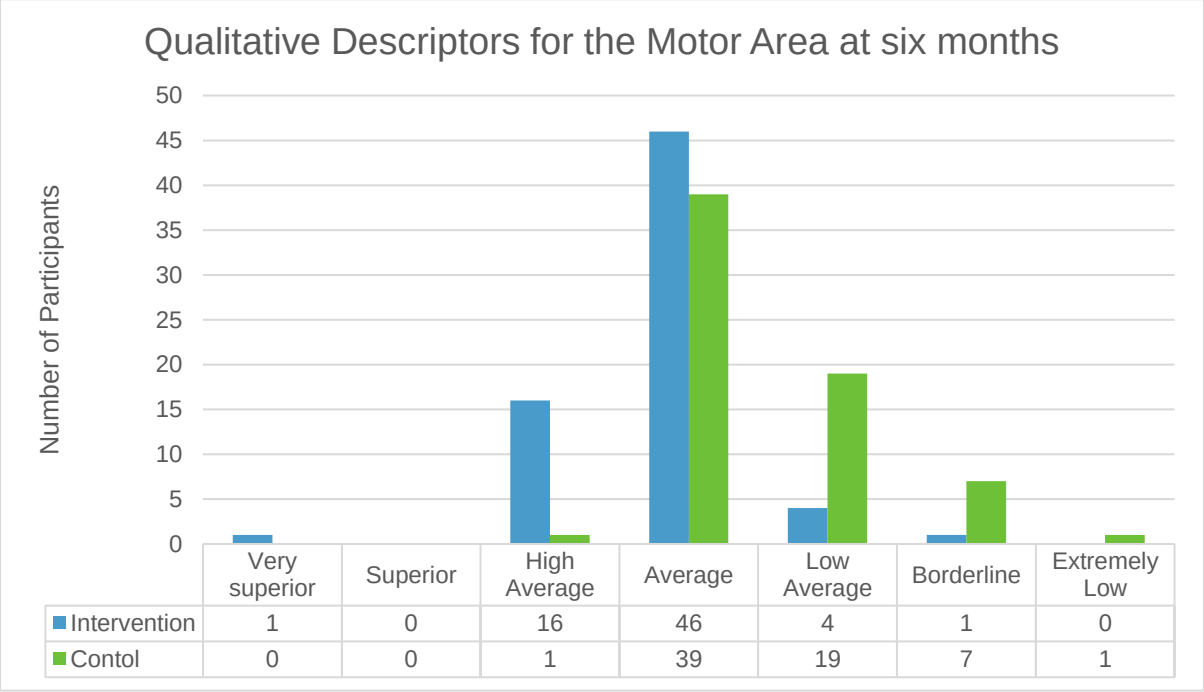
	Very superior	Superior	High Average	Average	Low Average	Borderline	Extremely Low
Intervention	0	2	0	60	1	0	0
Contol	0	2	0	55	9	0	0

From the figures 5.8 – 5.10 we can see how the experimental group tested at higher levels and shows how in this area EI may add value. Only one child was referred for speech therapy from the entire sample size. The referral given was at age six months in the intervention group.

5.7 Qualitative Description of Motor Composite Scores

Figures 5.12 – 5.14 documents the number of subjects falling into each category for the motor section at all three testing ages.

Figure 5.12 Qualitative Descriptions for the Motor Area at six months



	Very superior	Superior	High Average	Average	Low Average	Borderline	Extremely Low
Intervention	1	0	16	46	4	1	0
Contol	0	0	1	39	19	7	1

Figure 5.13 Qualitative Descriptions for the Motor Area at 12 months

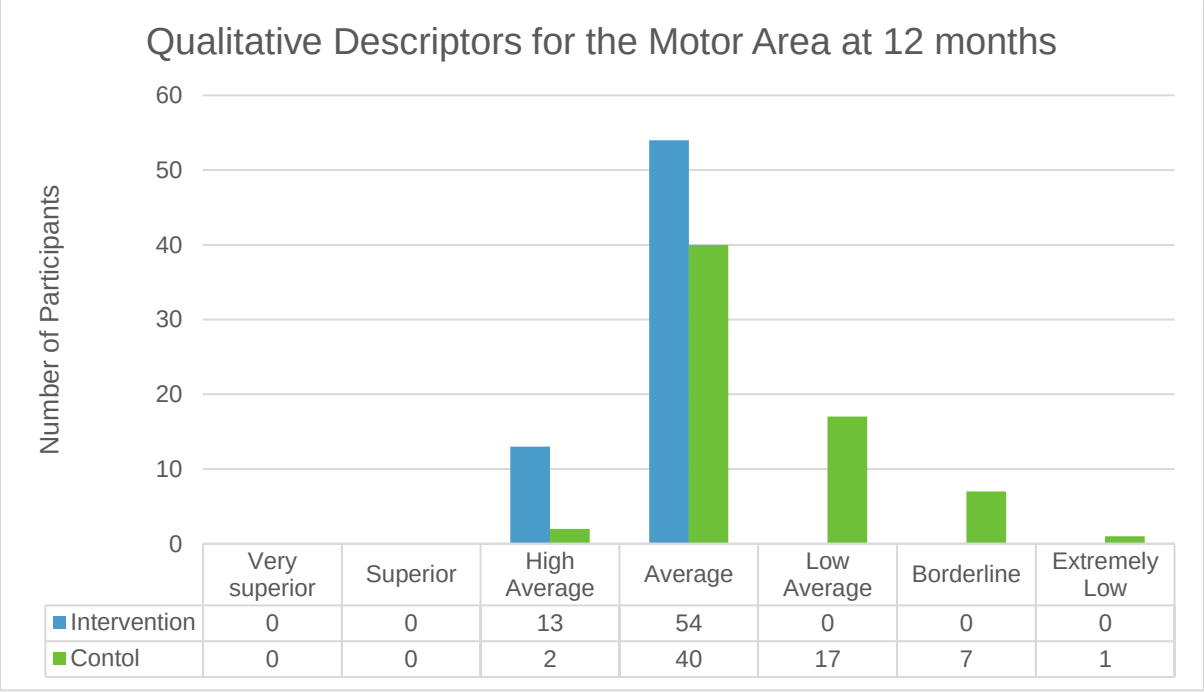
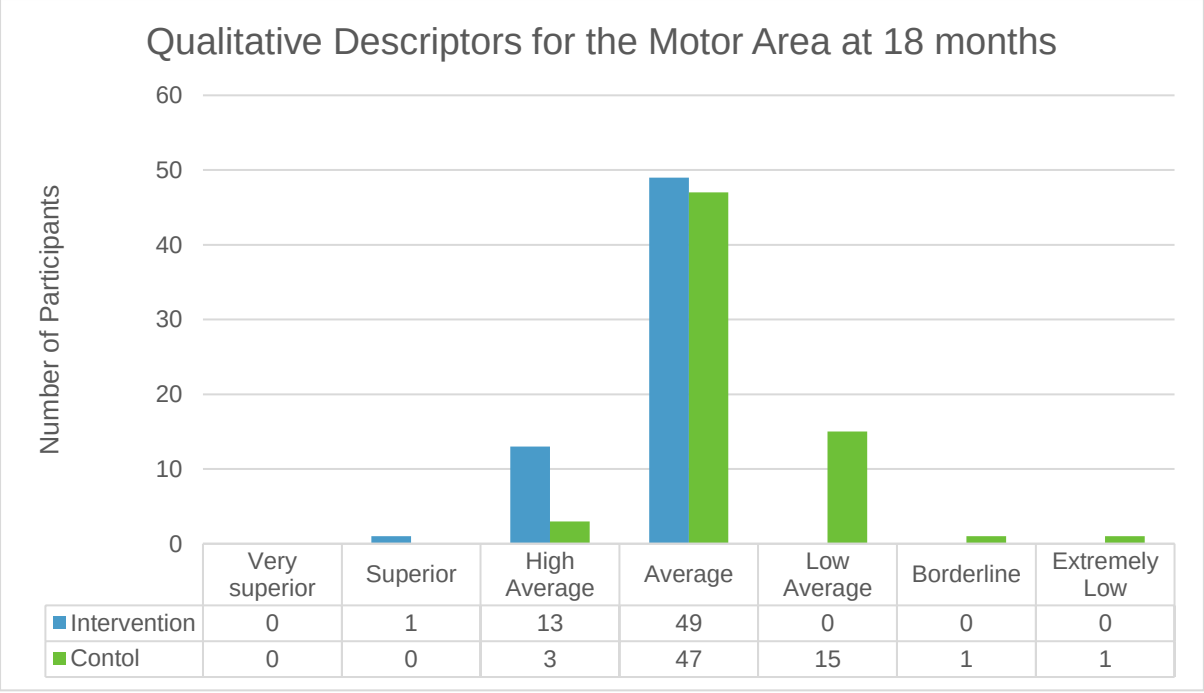


Figure 5.14 Qualitative Descriptions for the Motor Area at 18 months



From the figures 5.11 – 5.13, we can see how the experimental group tested at higher levels and shows how in this area EI may be of benefit. The children who needed referral for motor delay were referred to another physiotherapist to ensure that there

was no skill transference based on the testing items. At testing age six months, one child from the experimental group and eight from the control group were referred. At 12 months there were eight participants from the control group referred. At 18 months there were two infants from the control group referred.

5.8 Conclusion

Despite the control and experimental groups being well matched for gestational age, there was a significant difference in motor development at all tested ages. There was a significant difference between the groups in language development at both 12 and 18 months. There was also a significant difference in cognitive development at six months between the groups. The Scaled six and 12-month motor and language scores were predictive of the 18 month results.

These findings show that that over the 18-month period the group which received intervention had significantly better developmental scores.

Chapter 6: DISCUSSION

In this chapter, the results that were obtained in this study will be discussed. The results will be compared to those recorded in previous studies. The implications and limitations of this study will be highlighted, and recommendations will be made.

The results of this study addressed the aims and objectives set out at the commencement of this study. The aim of this study was to design a programme for developmental care and assess the effect of the programme. The NICU programme was developed using the modified nominal group technique. The developmental statuses of the participants who received the programme, as well as the participants who did not receive the programme was established. This developmental information was analysed to assess the effectiveness of the programme. The demographic and additional medical information was also analysed to assess whether it had an impact on the results.

6.1 BSID III Scores

The BSID III test was administered to obtain developmental information in the three developmental areas of motor, cognitive and language development. This data was used to compare the two groups to assess the differences found between the two groups.

6.1.1 Motor Development

The composite motor scores at six, 12 and 18 months for the experimental group all showed statistical significance in the area of motor development with the experimental group performing better at all three testing points. This is a similar result as was obtained in several studies conducted in other countries looking at various EI programmes on premature infants (Blauw-Hospers et al., 2007; Oberg et al., 2012; Spittle et al., 2015; Ustad et al., 2016). This study has confirmed early intervention physiotherapy consisting of massage and joint compressions delivered in the NICU can have a positive impact on the motor development of an at-risk premature infant and that the effect is seen early and maintained at 18 months. Similar results were seen in various studies conducted on established programmes such as NIDCAP,

Kangaroo Mother care (KMC) and music therapy, the training for most is not readily available in South Africa (Bieleninik and Gold, 2014). These studies range in gestational age (27 – 41 weeks), age at assessment (3 – 24 months) and intervention type. The common aspect is that there was early physiotherapy intervention. The common interventions included were different combinations of massage, parent education, NICU modulation, positioning, KMC, passive movements and movement facilitation (Hughes et al., 2016; Oberg et al., 2012; Shapiro-Mendoza et al., 2013; Peters et al., 2009; Wu et al., 2014b; Als et al., 2004). The current study used a combination of techniques from these various programmes.

Studies that looked at massage with KMC and parent support showed significant improvement in development scores up till the testing age of two years, with the motor component showing the most improvement in the period of three to six months (Hughes et al., 2016). Our study, which incorporated massage, showed improved motor scores at all three testing ages. In the studies that follow the NIDCAP model there was a significant improvement in motor developmental scores of $p=0.017$ at age 18 months (Peters et al., 2009). These programmes use the NICU modulation, positioning and KMC in their studies. When compared to our programme the common intervention was the positioning. The study protocol uses massage, passive movements and movement facilitation showed improved motor developmental scores at all testing ages up to the age of two years (Oberg et al., 2012). The current study used various intervention aspects of all of these studies. The results that were obtained during the study showed improved motor developmental scores at all three testing ages.

Oberg, 2012, documented a study protocol with a musculoskeletal component also consisting of joint compressions on 150 preterm infants that could be used to improve motor outcomes (Oberg et al., 2012). In a systematic review done in 2016, a total of 36 trials were included that met the inclusion criteria. These studies assessed the effectiveness of EI on the motor development of infants with gestational ages from 24 to 36 weeks. There was significant improvement in the motor development of these infants up to the age of 24 months. The studies that they included in their systematic review used interventions similar to the current study, those being positioning and passive movements. The intervention that was different was that of movement

facilitation (Hughes et al., 2016). This was a similar result to our study as the current study showed a significant difference in the motor development of the experimental group. The regression analysis also showed that the treatment was a significant factor in the 18 month motor results. It has been shown that the corpus callosum in preterm infants is under-developed when compared to that of full-term infants. This will have an effect on motor development, sensory processing and coordination due to the fibres that link to two hemispheres (Thompson et al., 2011). As this programme has been shown to improve motor development, the possible negative effects of an under-developed corpus callosum can be improved.

Passive movements with joint compressions were done during this developmental programme. Motor skill development has been shown to be dependent on the development of the somatosensory system. Proprioceptive sensation is required to develop appropriate motor skills (Cascio, 2010). Joint compressions are a treatment technique that stimulate the proprioception sense (Barton et al., 2015). The brain uses information from the proprioception sense as the early stages of movement analysis (Cullen, 2012). In a functional MRI study conducted on premature infants it was found that proprioceptive and tactile stimulation of passive movements, joint compressions and massage activated the corticospinal tracts through the thalamus and brain stem. These carry the voluntary muscle movements (Arichi et al., 2010). All of the techniques in that study were included in ours. This can be linked to the better motor developmental outcome at all testing ages in the experimental group. Exercise in premature infants has been shown to cause an increase in insulin like growth factor-1. This leads to an increase in bone formation which allows for improved motor movement (Field et al., 2010).

Massage was one of the components of the developmental programme that was tested. Massage has been shown to promote weight gain in premature infants and is therefore associated with shorter NICU stay (Taheri et al., 2018) . The main reason that has been shown for this weight gain is due to the stimulation of the baroreceptors. This activates vagal nerve activity and causes food absorption hormones to increase (Taheri et al., 2018). With a shorter NICU, stay there is less stress on the infant. Less stress levels have been shown to improve developmental scores (Ramachandran and Dutta, 2013). A study conducted on the efficacy of a short duration of massage in

NICU showed that even a five day massage course had these positive effects on 45 premature infants that were studied (Taheri et al., 2018). Massage has been shown to decrease the stress hormone cortisol (Taheri et al., 2018; Abdallah et al., 2013; Wang et al., 2013; Saeadi et al., 2015). Elevated cortisol, in response to stress, can distort foetal brain development and body development. This negatively impacts on motor development (Kesavan, 2015; Buss et al., 2012; Belsky and de Haan, 2011). Increased cortisol levels can lead to accelerated neuron loss, myelination delay and can interfere with neurogenesis (Belsky and de Haan, 2011). For this reason, massage is a technique that can be effectively used to combat the increased cortisol levels and therefore improve motor development in premature infants. Another possible reason for the improved developmental scores is that massage has been shown to accelerate encephalographic activity maturation in preterm infants (Santos et al., 2015). It has been shown to aid in central nervous system maturation by helping to normalise function and increases the secretion of neuroendocrine substances that are needed for the infant's growth. This improvement that is shown has been found in motor, cognitive and language developmental outcomes (Badr et al., 2015).

The BSID III, as previously described, provides feedback on both fine and gross motor developmental areas. This study showed significant differences with p values <0.001 at all testing ages in both motor areas in the experimental group. In a systematic review done on 25 randomised control trials looking at the effects of early intervention, it was shown how early intervention has a positive effect on both areas of motor development. This review concluded that these positive effects were still apparent at 36 months of age (Vanderveen et al., 2009).

The human brain has been shown to be plastic and change occurring due to various experiences (Oberg et al., 2012; Van Hus et al., 2016). For this reason, motor development can be highly influenced by early intervention. The current study has had a similar positive influence on motor development as the established developmental programmes (Peters et al., 2009; Blauw-Hospers et al., 2007). A longitudinal, randomised control trial was conducted on 176 premature infants of gestational ages <32 weeks and birthweights of <1500g, showed that early intervention had positive effects on motor development up to the age of five years. This was attributed to the early experiences that the intervention offered to the developing brain (Van Hus et al.,

2016). The short-term results of this study showed similar results to the current study reinforcing the need for early intervention for positive effects on motor development. The regression analysis conducted in this study showed that the EI treatment received was a predictor of better developmental outcome in the group of infants studied.

Positioning is an important aspect of NICU developmental care and is done to facilitate musculoskeletal development in this at-risk population group (Sweeney and Gutierrez, 2002). The main objectives during positioning that have been proposed are: ensuring that skeletal development continues to its optimum; to allow for proprioceptive input and to promote calming and regulating behaviour in the preterm infant (Toso et al., 2015; Roan and Bell, 2017; Nightlinger, 2011). This study aimed to increase the physiological flexion and the containment of the infant with the positions used. Positioning has been shown to decrease the asymmetry that is found in premature infants. This aids in improving the motor development as infants are able to use their musculoskeletal system more effectively, as less asymmetry can lead to improved muscle strength, reflexes and muscle tone for early development (Madlinger-Lewis et al., 2014; Sweeney and Gutierrez, 2002; Maguire et al., 2009a). Motor activity that is smooth, combined with an infant who is able to self-regulate their own behaviour are seen as indications of good physiological stability and motor control from four months of age (Roan and Bell, 2017; Rothbart et al., 2011). With the improvement in all these musculoskeletal functions it links to the reason why there was an improvement in motor development scores. The control group was receiving standard NICU care which, according to the unit protocol involves positioning and occasionally KMC. The problem however, is that there is no standard protocol in either unit as to how this is done.

6.1.1.1 Factors Predictive of Motor Development

The regression analysis conducted on this study showed that in the study population there were three factors predictive of the motor outcomes. These factors were the treatment, gestation and IVH. These are similar to studies conducted on premature infants investigating their development. A two – six-fold increase risk of poorer developmental outcomes was seen in premature infants with IVH (Aylward, 2014; Stephens et al., 2010). It has been well documented that the lower the gestational age

the higher the risk of poorer motor outcomes (Dueker et al., 2016; Li et al., 2016; Schonhaut et al., 2015; De Jesus et al., 2013).

It was identified via the regression analysis that was conducted on the control group's data set that gestational age and NEC were the factors predictive of motor outcome. This was a different outcome to the study conducted on 157 VLBW infants who were followed-up at the age of four years. This study discovered that NEC was not a predictive factor of motor outcome. Their study showed that low birth weight was the predictive factor (Zwicker et al., 2012).It was however, a similar outcome to a study conducted on 1155 premature infants ranging from 23 to 27 weeks gestational age. This study showed an increased risk of motor developmental complications in infants who suffer from NEC (Martin et al., 2010).

The control group had participants that required referrals for therapeutic interventions based on their results on the BSID-III. At six months eight participants were referred for physiotherapy, eight at 12 months and two at 18 months. This is a confounding factor in this study as it may have impacted the control group results. The data from these participants were included in the results and subsequent testing ages. This has been listed as a limitation of the study.

6.1.2 Cognitive Development

This study showed a significant difference in the experimental group in cognitive development only at the six-month follow up. The cognitive items which the BSID-III assesses at six months have a strong motor aspect to them. They require infants to move items and engage various muscles to complete the required tasks that could lead to the significant difference in the cognitive scores at six-months. At 12 and 18 months, the composite scores were higher for the experimental group but not significantly so. The scaled scores showed significant difference at all three testing ages in the cognitive section. The link between motor development and future cognitive development has been established by investigating attention and executive functioning that are related to motor performance, with cognitive and motor function development being parallel in children (Wassenberg et al., 2005). It has been shown that early motor development improves long term cognitive development. It is suggested that motor skills are a prerequisite for learning skills such as perceptual and

cognitive skills. It is also proposed that sensorimotor experiences are important when combined with activity for the development of cognitive skills (Piek et al., 2008). It has been shown that motor activity increases neurotransmitters in the brain which then allows for improved cognitive development (Fedewa and Ahn, 2011). This can be the reason for the improved results in the cognitive developmental area in the experimental group.

A systematic review done by Spittle (2015) investigated the effect of early intervention programmes. The researcher reported a variety of outcomes ranging from significant results in cognitive skills to no significance reported. This review only included studies where the intervention was started post-discharge. The interventions included were positioning, neurodevelopmental therapy (NDT) and environmental modifications. These results showed improvement in cognitive skills during infancy (Spittle et al., 2015). The gestational ages in the Spittle study (2015) range from 28 to 36 weeks, which was a similar range to the current study. A different study conducted on premature infants born between 30- and 36-weeks' gestation in Oslo, showed no effect on cognitive development following early intervention consisting of KMC, massage and NICU modulation. They attributed this to the possibility of the programme being less beneficial for moderate and late premature infants (Kynø et al., 2012). These interventions were part of the current study programme and can aid in explaining the results that were obtained in the cognitive developmental area of the test.

A more encouraging outcome was found in a study conducted on 178 Taiwanese VLBW premature infants. This study found positive effects on cognitive development at 24 months. The interventions used in this study included massage, NICU modification, positioning and parent education (Wu et al., 2014b). Similar results were found on 128 premature infants who were tested up to 36 months of age and they were found to have positive impact on cognitive development. This study included any premature infant that received any type of EI. The treatment modalities were not listed specifically (McManus et al., 2012). These studies again draw a link to the current study programme including some of these interventions and also show improved cognitive developmental scores.

Massage is a technique that was used in this study. Cortisol levels have been shown to be increased in premature infants (Abdallah et al., 2013; Field et al., 2011). Increased cortisol levels can cause destructive changes to the hippocampus (Asadollahi et al., 2016). The hippocampus is important for converting short term memory into long term memory as well spatial relationships (Persson et al., 2005). Massage decreases the stress hormone cortisol (Álvarez et al., 2017). For this reason, we can see how massage can play an important role in the cognitive development of a child. This study only followed the infants until the age of 18 months, when no long-term memories have been stored yet. This could be part of the reason as to why there was not a significant difference noted at the 12 and 18 month ages. Massage has also been found to stimulate insulin-1 growth factor in premature infants. This hormone is associated with brain growth regulation (Guzzetta et al., 2011; Field et al., 2010). This hormone has a role in the development, differentiating and plasticity of the nervous system (Benarroch, 2012). These processes are all vital in the development of the cognitive system in an infant This may be a reason for the results seen at the six-month testing age.

Massage has been shown to decrease stress levels in premature infants (Smith, 2012). Stress causes the activation of the sympathetic portion of the autonomic nervous system. This causes cortisol to be released. Cortisol causes increases in heart and respiratory rate as well as causing a decrease in the uptake of the hormones that aid in digestion and growth (Anderson and Patel, 2018). Stress can also hinder the process of neurocognitive learning and sensory interpretation (Blair, 2010). As massage decreases the levels of stress that premature infants suffer, it shows that it will also improve the cognitive outcomes in this population group. Massage has been linked to showing a positive impact on the neurobehavioural development of preterm infants. This development has been shown to be delayed in premature infants admitted to NICUs. This can be due to the various external sensory stimulations including lights and sound. Massage has been shown to aid in the infant's sensory system being able to regulate these sensory inputs, which in turn aid in the child being in a calmer state in order for more active learning to occur (Milgrom et al., 2010; Aliabadi and Askary, 2013). This may be a linking factor as one of the intervention techniques in the current study is massage and may be part of the reason as to why

the intervention group also showed improvement to the cognitive developmental scores.

There has been a strong link between early gross motor developmental problems and later issues in executive functions such as processing speed and working memory (Koziol et al., 2012). A study conducted on seven to 12-year olds showed the correlation between learning disabilities and locomotor skills as well as object control skills. There was also a link found between reading and locomotor skills and mathematics and object control skills (Koziol et al., 2012). Complex information is processed, and the final product is brought about by the joint work between the complex motor skills such as gesture, speech, writing or typing. For this reason, motor development and cognitive skills are linked (Koziol et al., 2012). This may also be a reason as to why there was cognitive and motor skill improvement following this study in the experimental group.

The positioning of an infant is an important technique as it allows the infant to develop the muscles required for head and neck control as well as postural control. This is achieved by allowing the infant to mimic the position that the infant would have assumed in utero and are important in the attainment of cognitive skills (Nightlinger, 2011; Dudek-Shriber and Zelazny, 2007). Positioning has been shown to improve an infant's self-regulation (Zarem et al., 2013). Physiological flexion allows the infant to support the self-regulatory movements of bringing hands to mouth that allow the child to self-sooth (Roan and Bell, 2017). High levels of glucocorticoids and catecholamines have been shown to be released when a premature infant undergoes stress. These hormonal increases can cause deficits in executive function and therefore have a detrimental effect on cognition. A decrease in cognitive developmental scores have been shown to be linked to increased glucocorticoid levels in premature infants (van der Lugt et al., 2010). The current study shows a significantly better cognitive function following the use of positioning as part of the intervention techniques with the intervention group. The physiological improvements due to positioning could help explain why the intervention was successful. As there is no standard of practice protocols on positioning in the control group's unit, we are unable to say with certainty whether this was a factor or not on its own.

It has been shown that children are born with and develop basic discrimination skills early in life. These include skills that help them learn about people. Actions include, turning their head to look for a face or sound. In the first two years of life infants learn to discriminate between different facial expressions and learn the ability of eye gaze (Flavell, 1999). Eye gaze is a process that is required for motor skill acquisition as well as language milestones (Vickers, 2011; Flavell, 1999). An infant is also able to imitate motor skills, for example sticking a tongue out. This occurs from an early age as well. This again requires the cognitive and motor skills to work together to reproduce the movement (Flavell, 1999). These skills all link together in the different developmental domains as you need motor skills to be able to turn your head. This intervention programme showed an improvement in both motor and cognitive testing areas and this is due to the fact that these areas work in partnership to produce the required movements and cognitive processes.

Early in an infant's life they learn how to differentiate between people and objects. This process is known as intentionality. This is the process of how a person reacts to and thinks about the difference between an object and a person. These skills develop initially with the motor, sensory and language areas. A child will for example examine a block with the fingers. They feel it often by mouthing the item and then vocalise at the item. Objects react differently to people and this allows the infant's cognitive system to relate to the intentionality of an object (Flavell, 1999; Waytz et al., 2010). This programme aids in this with the massage and positioning interventions of this study that aids the sensory system in the ability to self-regulate allowing for improved functioning (Hofmann et al., 2012).

6.1.2.1 Factors Predictive of Cognitive Development

In the regression analysis performed on the cognitive developmental data from the study population, treatment, surfactant and gestational age were found to be the factors predictive of cognitive development. This is a similar result found in a study conducted on 1667 premature infants tested at 18 months. They also found that gestational age was predictive of cognitive outcomes (Schonhaut et al., 2015). Another study conducted on 6150 premature infants ranging from 24 to 36 weeks gestational age, were followed up at age two. They also concluded that gestational age was a predictive factor for cognitive outcomes (Richards et al., 2016).

Cognitive development varies greatly from birth to 18 months. This study programme works on various aspects of that development and shows an improvement in the developmental scores at the three testing ages.

6.8.3 Language Development

This study showed significant differences between the experimental and control groups in the composite scores at both 12-month and 18-month testing ages in the expressive language area with the experimental group recording higher developmental scores. The lack of significant results at the six-month age could be due to the nature of the testing items at that age. They are based more on vocalisations than that of motor-related language activities. The receptive language scores showed significant differences at all three testing ages. The 12-month results showed scaled scores of 14.2 and 13.8 for the experimental and control groups respectively. At the 18-month testing age, the experimental group showed a score of 10.3 versus 9.5 in the control group. These results could be due to the nature of the testing items. These items rely on motor abilities such as head turning or pointing various items out. This could explain the variations in the results. It was discovered that there is an excitation in the hand motor area in the language dominant hemisphere (Meister et al., 2003). This link has been shown to be greater between six and eight months (Björn et al., 2012). This shows the link between the language and the motor development demonstrating why the language development improved following the implementation of this EI programme.

This is the same result as was obtained by a randomised control trial conducted on 109 infants. They found early language skills were improved following early in-NICU intervention consisting of massage, KMC and NICU modification (Milgrom et al., 2013; Newnham et al., 2009). This study stated that language skill development was integral for later academic achievement. The programme tested involved that of touch which links to the massage portion of the current study (Milgrom et al., 2013). Premature infants who receive massage in the NICU have improved motor skills and this includes the speech muscles (Sohr-Preston and Scaramella, 2006). Language development is associated with motor development. The areas include that of manual gestures, oral-motor ability and gross and fine motor skills (Alcock and Krawczyk, 2010). Massage

has been shown to improve a premature infant's information processing in the auditory-visual area by allowing the infant to self-regulate through the repetitive motions (Feldman and Eidelman, 1998). Language skills develop from good auditory skills (McMahon et al., 2012; Bailey and Snowling, 2002). For this reason, the massage aids in language development in this study population.

The act of sucking, feeding and speech production are all processes that involve the overlapping of neural networks of the cortical, subcortical and brainstem regions that relate to the motor developmental areas (Koziol et al., 2012; Poore and Barlow, 2009). It has been shown that the language and motor systems overlap. This collaboration of developmental areas is demonstrated by hand gestures that accompany speech (Meister et al., 2003). In the study conducted by Meister et al, 2003, they tested the link between the hand motor area in the cortex and reading. They found on MRI that this area responded while the reading was taking place. They hypothesised that this occurs due to the existence of mirror neurons that activate during observation and performance of certain tasks such as grasping objects. The area of the brain that these neurons are found in is linked to Broca's area. They further state that this allows the strong link between action and communication allowing the development of the motor and language systems to be linked (Meister et al., 2003). The current programme has a strong sensorimotor component. It has been shown that there is a link between the sensorimotor and speech perception in six month olds (Bruderer et al., 2015). This shows how this programme can aid in development of language skills in this population group. It has been shown that infants who for example are able to sit can freely turn their heads to engage in surroundings and in this way, begin to vocalise more and engage in their environment better (Björn et al., 2012; Iverson, 2010). The programme presented in this study has shown that it improves motor developmental outcomes. The experimental group was able to achieve their milestones timeously and this allows for the infants to engage in their environments in a more meaningful manner.

Our study showed the same positive impact of early intervention on language skills as numerous other studies confirming that early intervention is a necessary aspect of a premature infant's management. The interventions that were similar in these studies were that of massage, positioning and joint approximations (Shapiro-Mendoza et al., 2013; Blauw-Hospers et al., 2007; Nordhov et al., 2010). A study in 2007, investigated

whether EI programmes based on motor interventions would have a positive impact on cognition and language development. The study found that in 22 of the 26 studies there were positive effects on the cognitive and language development following EI aimed at motor development. This shows again the EI is important for all developmental areas of premature infants. The interventions used in this review included the NIDCAP programme, massage, positioning and maternal education (Blauw-Hospers et al., 2007). Another study also highlighted the need to monitor and assess late preterm infants as they are also classed as 'at-risk'. These infants are reportedly often discharged and not followed up (Shapiro-Mendoza et al., 2013).

It has been shown that there is improved language development when a bimodality approach is used in intervention. These studies used massage, positioning, NICU modification, KMC, oral stimulation and joint approximations (Gabis et al., 2015; Jobe, 2014; Kanagasabai et al., 2013; Björn et al., 2012; Vaivre-Douret et al., 2009). This can explain why the various modalities used in the current study had such a positive effect on the language developmental scores. With the passive movements and joint compression there was the tactile input of the massage added to this. Facial massage and sensory stimulation have been shown to have a positive influence on feeding ability and this allows for improved weight gain (Björn et al., 2012; Vaivre-Douret et al., 2009). The multisensory impact has also been shown to improve feeding and reduce the hospital stay (Kanagasabai et al., 2013).

The positioning of an infant is important as it allows the infant to develop the muscles required for head and neck control as well as postural control. This ability is required for the infant to learn the suck-swallow-breath pattern which is required for adequate feeding in a neonate (Picheansathian et al., 2009). These positions are all important for the development of language skills (Dudek-Shriber and Zelazny, 2007). It was also shown that positioning in the NICU plays an important role with self-regulation. Positioning promotes neurobehavioural development, which promotes communication development (Greenlee, 2013). Positioning of a neonate has been shown to decrease stress. Stress related to feeding can cause altered sensory-motor pathways to form (Shaker, 2013). According to the Dynamic system model of feeding, stability of the physiological system allows interaction between the infant's arousal, posture, movement and self-regulation. When these various systems are in sync there can be

adequate feeding in the suck-swallow-breathe feeding manner (Shaker, 2013). Positioning has been shown to improve self-regulation, the musculoskeletal system and therefore aids in the improvement of both feeding and communication.

6.1.3.1 Factors predictive of language development

In the regression analysis performed on the language developmental data from the experimental group, treatment and surfactant were found to be the factors predictive of cognitive development. The literature search conducted for this study could not find any research conducted on the impact of surfactant on language development. The control group's regression analysis conducted on the language scores data set showed that only surfactant was a predictive outcome of the results.

Language development is one of the developmental areas that this study had a positive impact on in the experimental group. The various aspects of this programme have aided this population group in obtaining significantly higher developmental scores in this developmental area.

6.2 Demographic Characteristics

6.2.1 Gestational Age

The mean gestational age in this study in the control group was 32.5 weeks versus 32.8 in the intervention group. The groups were well matched for gestational age with a p=0.53. The experimental group had 19% of infants of a gestational age lower than 32 weeks, versus the control group of 20%. This shows that the range of gestational age was also well matched. The regression analysis conducted on the results demonstrated that gestational age was a significant factor associated with developmental outcome in both the experimental and the control group at 18 months. This finding is not surprising as it has been well established that prematurity is a risk factor for poor developmental outcome (Aylward, 2014; Peacock et al., 2012; Hoekstra et al., 2003). Lower gestational age has previously been found to be associated with lower developmental scores in all facets of development. This is thought to be due to the fact that the brain development is directly related to gestational age. This is been said to be due to the under-developed pre-term brain which is only at 53% volume when compared to a full term infant brain (Chawla et al., 2016; Glass et al., 2015;

Moore et al., 2012a; Kinney, 2006). The gestational age of an infant is directly proportional to their development which is also seen in this study.

6.2.2 Birth Weight

The groups were well-matched with regards to the mean birth weight, with the intervention group being 1823.10gr (± 560.78) and 1811.00gr (± 580.06) for the control group. It has been documented that premature infants who fall in this birthweight category have a greater risk of suffering from developmental delay in all three developmental areas that were tested at 18 months, with a 3.01 odds ratio for developmental delay (Schonhaut et al., 2015). The developmental areas tested included motor, language and cognitive skills (Schonhaut et al., 2015; Vohr, 2013). It has been shown that the weight of a brain of a child born on this weight class is only 60% when compared to a full term infant and is at a critical period of brain development (Vohr, 2013). This study had the opposite result as a systematic review conducted on a birthweight range of 1500g to 2000g (McGowan et al., 2011). The current study found no independent association between birthweight and the outcome of the study as it was not a variable in the regression analysis.

6.2.3 Sex

The male-female ratio was also well matched for both groups with a near-even distribution of male to female infants. The male:female ratio in developmental delay has been shown to be 2:1 (Polyak et al., 2015; Jacquemont et al., 2014). This has been attributed to the Female Protective Model. This is said to be an occurrence that allows the female sex gene to protect the female infant from mutations more effectively than in males (Robinson et al., 2013; Jacquemont et al., 2014). The male foetus is said to have a greater exposure to androgen and Mullerian inhibiting substance. This substance decreases the production of surfactant, which can explain a reason why male infants have poorer outcomes when compared to females (Peacock et al., 2012). In the regression analysis run on the data from the current study, it was found that sex was not a significant factor in the results reasons for this are unclear and could be investigated further.

6.3 Mechanical Ventilation requirements

The intervention group showed a 30% rate of biphasic ventilation versus 47% in the control group. This was in contrast to oxygen therapy use via nasal cannula being 91% in the intervention group as opposed to 43% in the control group. Mechanical ventilation has been shown to be associated with higher mortality and increased morbidity in pre-term infants especially regarding the cognitive domain (Jiang et al., 2015; Breeman et al., 2017). The intervention group had less invasive mechanical ventilation with better outcomes. Less invasive mechanical ventilation has been to shown to be very effective on decreasing BPD, the risk of IVH and therefore an improved neurological outcome (Flannery et al., 2016). Premature infants who have BPD have been shown to suffer for a greater risk of developmental difficulties in all developmental areas (Morley et al., 2008). CPAP Has also been shown to decrease the risk of BPD in premature infants and therefore decrease the risk of subsequent developmental delays (Patel and Greenough, 2008). It has also been shown that infants who receive less invasive mechanical ventilation show fewer days on ventilation leading to improved developmental scores (Morley et al., 2008).

The other significant difference between the two groups in the study was length of ventilation. The median for the intervention group was one day as opposed to two days in the control group. A retrospective study conducted on 5364 premature infants showed how longer ventilation was significantly associated with lower developmental outcomes (Walsh et al., 2005). In a retrospective study conducted on 404 premature infants below 30 weeks GA, it was shown that infants who had shorter length of mechanical ventilation had better neurodevelopmental outcomes at 24 months (Vliegenthart et al., 2017). Infants with a longer history of ventilation are at greater risk and need to be prioritised for intervention. The difference between the two groups was only one day but may still have contributed to the better developmental outcomes of the intervention group. A study conducted to investigate premature infant stress levels on 107 premature infants under 32 weeks, showed that infants who were on mechanical ventilation for longer periods were at a greater risk for stress (Morag et al., 2017). This study also showed that infants who had greater stress levels had lower developmental scores at 12 months (Morag et al., 2017). Stress in the premature infant has been linked to decreased frontal and parietal brain width and abnormal motor behaviour (Cong et al., 2017). During the regression model building, ventilation

correlated with surfactant use and could not be included in the same model. All the above factors could have contributed to the better developmental outcomes in the intervention group.

6.4 Steroids

Maternal antenatal steroids are often indicated in weeks 24 – 34 to reduce the neonatal morbidity associated with pulmonary problems if a risk for prematurity exists (Murray et al., 2017). The use of antenatal steroid showed a significant statistical difference between the groups with the control group showing greater antenatal steroid use. Antenatal steroid use has been shown to be a possible cause of IUGR. The IUGR can lead to poorer developmental outcomes (Murray et al., 2017; Murphy et al., 2012; Peltoniemi et al., 2011). Studies have shown that repeated courses of antenatal steroids do not improve outcomes in preterm infants but rather can lead to an increased leukomalacia risk and poorer neurodevelopmental outcomes (Elfayomy and Almasry, 2014). This was thought to occur due to antenatal steroids altering the placental function which influences foetal growth (Elfayomy and Almasry, 2014). It has been well documented that premature infants who have foetal growth retardation have poorer neurodevelopmental outcomes (Li et al., 2016).

Both the control and the experimental groups were given one course of antenatally administered steroids if required. During the regression model building, steroid use was omitted as did not significantly improve the model. When removed the adjusted r squared improved, therefore improving the model. Antenatal steroids are dependent on timing for their efficacy. In a population-based prospective cohort study, with a sample size of 707 extremely pre-term infants, documented that the shorted the duration of the steroids prior to birth the less effective they were (Mackie et al., 2015). An aspect that was not documented in the current study was that of timing between the steroid administration and the delivery. This could be the reason there was not a clearer link between the steroid use and the results obtained.

6.5 Surfactant

The use of surfactant showed a significantly statistical difference between the two groups, with the control group showing more use. The result in this study showed that the control group who had a greater use of surfactant had poorer neurodevelopmental

outcomes. Surfactant is not considered a risk factor for poor developmental outcome in the general literature (Verlato et al., 2018). The medical information obtained did not show why the control group needed more surfactant use as there were no significant differences between the medical information of the two groups. There were no unit policies on the use of surfactant at the time of testing. The decision to give surfactant was based on the Paediatrician's assessment of each child.

The regression analysis demonstrated that surfactant was a significant factor associated with lower language and the cognitive scores but was not associated with the motor scores. In a matched-pair analysis of a large cohort study conducted on infants with a gestational age of less than 32 weeks, it was found that the use of less invasive surfactant showed shorter duration of ventilation and lower risk of BPD and chronic lung disease (Göpel et al., 2015). Chronic lung disease has been shown to be a reason for developmental delay (Laughon et al., 2009). In this study the surfactant was administered to the younger gestational age participants. This could be the reason as to why they are at risk for the lower scores as gestational age has been shown to be directly proportional to the developmental scores in pre-term infants (Glass et al., 2015).

6.6 Oxygen therapy

There was a significant difference between the two groups relating to oxygen therapy. The experimental group had a 91% use of oxygen therapy when compared to the control group of 43% use of oxygen therapy. These factors were also not found to be significant in the regression analysis that was conducted. Oxygen therapy was not included under time on ventilation. A study conducted on 810 preterm infants using various oxygen saturations showed that it did not impact growth velocity in this population group (Navarrete et al., 2016). With the improvement in medical services to this population group, the incidence of chronic lung disease has increased (Askie et al., 2003). This is thought to be due to the fact that the survival rate of ELBW premature infants are improving being on mechanical ventilation (Day and Ryan, 2016) Chronic lung disease is defined as continued dependence on supplemental oxygen at 36 weeks or 28 days of age depending on which was later (Roberts et al., 2017; Askie et al., 2003). The difference in oxygen therapy could be attributed to the fact that the control group was ventilated for longer than the experimental group. The

control group had a shorter duration of oxygen therapy but longer on mechanical ventilation. A study conducted on 60 preterm infants born at or earlier than 28 weeks, showed that when infants were weaned off NCPAP to nasal canulae it resulted in longer exposure to oxygen and required respiratory support. The study showed that the infants who were weaned straight from NCAP to room air had less time on oxygen therapy (Abdel-Hady et al., 2011).

In a study conducted on 253 preterm infants below 32 weeks gestation, it was found that there was no significant difference in BSID III scores at 24 months of age based on oxygen supplementation at birth (Boronat et al., 2016). Another study conducted on premature infants varying in gestational ages showed no significant differences in developmental scores in the BSID II when comparing oxygen supplementation (Glass et al., 2015). These are in line with the regression analysis results that were obtained for this study, where oxygen therapy was not found to have a significant effect on any of the results.

6.7 Complications of prematurity

The only area that showed a significant difference between the two groups was that of NEC. The control group showed a 4.3% NEC rate opposed to an 8.6% rate in the experimental group ($p<0.0001$). Despite having a higher incidence of NEC the experimental group in this study had better neurodevelopmental outcomes which is in contrast to the findings of Shah et al's (2008) study which included 192 premature infants which demonstrated a decrease in developmental score at two years of age following NEC at birth (Shah et al., 2008). The sample size in the Shah et al study had a mean gestational age of 27 weeks whereas the mean ages for this study were 32.5 and 32.8 weeks. In a meta-analysis conducted on 7843 premature infants, ranging in gestational ages, at the 20 month follow up it was found that 45% of the infants who had suffered with NEC had some form of neurodevelopmental delay (Rees et al., 2007). The lower developmental scores in infants who suffered with NEC have been attributed to the increased risk of malnutrition and the associated bacteria depending on the extent of the NEC (Martin et al., 2010; Soraisham et al., 2006).

In this study the proportion of infants that developed NEC in both groups was small. This is similar to a study done on 102 premature infants to determine which factors

have an impact on development (Rose et al., 2014). The mortality rate of NEC ranges from 10% to 50% of cases, with the smaller the gestational age the greater the risk of death (Hunter et al., 2008). The consistent factors for NEC development are that of prematurity and enteral formula feeding (Hunter et al., 2008). The type of feed the infants received is discussed next.

6.8 Feed type

There was a significant difference between the two groups with regards to type of feed used with these infants. The control group used breastmilk more as opposed to the experimental group who used formula feed more often ($p<0.0001$). The reason for the difference in choice of feed types is unknown. Further investigation into what informs feed choice is warranted. A limitation of this study was that it was not documented whether infants were exclusively breastfed or combination fed. The NICUs only documented the majority feeds on the charts. In studies conducted on VLBW premature infants, the use of breastmilk was associated with improved cognitive outcomes at seven years of age (Belfort et al., 2016; O'Connor et al., 2003). Large scale epidemiological studies have shown that early, exclusive breastfeeding is associated with higher IQ scores and improved cognitive functioning even when factors including birth weight and gestation are accounted for (Deoni et al., 2013). The infants' motor maturity was also linked to breastmilk due to the affectionate touch (Feldman and Eidelman, 2003). This has been shown to occur due to the calming effect that touch has on the infant's response to stress. Touch has also been shown to increase the infant's resilience in response to stress. These two mechanisms aid in motor maturity as the child is said to be in a calmer and more alert state (Feldman et al., 2010). This is a contentious issue as again the study does not differentiate between the act of breastfeeding and expressed milk being bottle-fed. Both the experimental and the control group were fed via orogastric tube and then a bottle once sucking was permitted. They either drank formula or breastmilk from the bottle. None were breastfed whilst in the NICU. It was not documented as to the method of feeding once the child was discharged. One of the main concerns with all the literature on breastmilk is that not many state whether the effects are a result of the breastmilk or the act of breastfeeding. In a pilot study conducted on 40 infants assessing the difference between the act of breastfeeding and expressed breastmilk showed no significant differences between groups when comparing growth measures (Bartok, 2010). There

have not been any studies published that assess the difference between developmental outcomes between breastfed babies and babies who receive breastmilk via bottle feeding. Most premature infants are fed via an orogastric or oronasal tube initially and only receive feed this way until they are able to suck. Our participants were fed via an orogastric tube until they were able to suck and were of an adequate weight. The units use the general rule of a minimum of 1.8kg before they will start attempting bottle feeding.

Premature infants who receive breastmilk have shown a lower rate of NEC and a shorter rate of enteral feeding than those who received formula (Cristofalo et al., 2013). There has been a connection made between breastmilk and the lower rate of gastrointestinal infection that affects many premature infants. This is thought to be due to the long chain oligosaccharide sugars which improve host defence and allow for gastrointestinal maturation (Schanler, 2011). The growth of pathogenic microbacteria due to the inflammatory response may contribute to the beginning of NEC (Shulhan et al., 2017). The experimental group had more formula feeding and had a greater NEC rate, which is in-line with these studies conducted. The regression analysis did not find a significant correlation between the developmental scores and the incidence of NEC even though the literature shows lower developmental scores. This could be due to the fact that relatively few infants developed NEC.

6.9 Sensory stimulation

Brain development is multi-faceted as has been demonstrated in the literature review. It involves the motor, cognitive, language, emotional as well as sensory systems. These systems are all connected and are linked during brain development (Graven and Browne, 2008b). As seen in the Dynamic systems theory, the various systems are all linked together for the overall development of the child and how the environment is so important for providing for experience to allow the brain to adapt and grow as needed (Philpott-Robinson et al., 2017; Thelen, 1989). For this reason the sensory system needs to be supported to ensure that the development of this at-risk population group is at its optimum as it impacts on all developmental areas (Philpott-Robinson et al., 2017). This intervention programme may aid in this process by allowing the infant to self-regulate by applying the massage and positioning interventions. It has been discovered that the sensory environment outside of the uterus is a challenge for a

preterm infant whilst going through a period of rapid brain growth and differentiation (McAnulty et al., 2009). It has been shown that positioning is a technique that allows this uterine environment to be mimicked (Picheansathian et al., 2009; Sathish et al., 2017). Positioning and massage were used in this programme to aid in the self-regulation of the infant. The control group also received positioning as a standard of care technique, but the specific position changes were not documented.

These systems are integrated during development and the development of the brain and structure is dependent on four aspects. The first is the genetic aspect of the brain development. The second is the internal brain activity which is aided by the rapid eye movement (REM) sleep cycle, third is the external experiences and stimulation of the sensory organs. Lastly, the physical, chemical, sensory and emotional environments (Graven and Browne, 2008b). EI has a role in three of these areas. The study combined techniques of massage, passive movements and joint compressions and positioning to possibly aid in this regard. The internal brain activity area is stimulated by allowing the baby more REM sleep. This has been shown to improve when the child is positioned properly in the NICU. Adequate positioning not only aids in improved postural control but facilitates improved sleeping patterns (Graven and Browne, 2008b; Madlinger-Lewis et al., 2014; Vaivre-Douret et al., 2009). Massage also aids in the improvement of sleep cycles and therefore this programme may aid the development of the sensory system from that aspect as well. In a study conducted on 50 LBW premature infants assessed the effect of massage on sleep. Massage was shown to improve the alertness in the sleep/wake cycle and enhanced the circadian rhythms of the premature infant (Kelmanson and Adulas, 2006).This programme uses positioning and massage as techniques therefore may improve the infant's REM sleep pattern and postural control.

Sensory stimulation has been shown to have numerous positive effects on this population group. In a study conducted on 50 premature infants ranging from 28 – 36 weeks gestation showed positive neurodevelopmental outcomes in all areas following a multi-sensory EI programme. It was found that the development of musculature tone was attributed to the proprioceptive stimulation and the positioning techniques used (Kanagasabai et al., 2013). These techniques were also used in this study and showed a positive effect in the developmental scores. The numerous positive benefits include

that of weight gain, improved feeding, improved rest-wake cycles as well as improved development in all areas (Vaivre-Douret et al., 2009). It has been shown that if we provide these infants with sensory input, as the current study does, it aids the adaptive responses that allow sensory integration to occur and that are needed for the correct functioning of the postural and movement coordination systems (Cabral et al., 2015). These are the many reason why research is now pointing towards positive sensory experiences for preterm infants to optimise function (Pineda et al., 2016). Massage, positioning, joint compression and passive movements used in this study all provide positive sensory input which may have contributed to the improved developmental scores that were obtained.

It has been stated that all of the sensory systems, with the exception of the visual system, needs outside stimulation for development in a premature infant (Graven and Browne, 2008b; Gabis et al., 2015). Jobe, 2014, stated how the neurosensory system is at risk of deprivation which is harmful to the plasticity of the developing brain (Jobe, 2014). The massage technique may aid in the skin receptors being activated. The positioning may allow for self-regulation of the infant to be improved. The passive movement and joint compressions may activate the proprioceptive system. These intervention techniques may work together to improve the sensory developmental domains of the infant.

6.10 Early Intervention

Early intervention has the primary goal of advancing learning and developmental areas (Lobo et al., 2013). Early intervention has been shown to aid in improving all developmental areas of a premature infant's life (Sarapuk et al., 2017; Hadders-Algra, 2011). One thing that the various programmes have consensus on is that the earlier the programme begins the better the effect. The other aspect is that it has been shown that prior to term age the main aim of EI is to diminish the stress in the preterm infant's life (Hadders-Algra, 2011). This links well with our programme as the aspects of the programme such as the massage allow for this to occur (Hernandez-Reif et al., 2007). There are numerous EI programmes which are available in various countries for a cost of both the training and the programme requirements. There is also no clear outcome in the literature as to which EI programme has the best effects (Lobo et al., 2013).

The NIDCAP programme has been shown to facilitate brain development. The study done by McAnulty in 2009, showed the differential vulnerability of the frontal region of the brain as well as improved right hemisphere functioning at eight years of age in a preterm infants can be opposed by implementing an EI programme for this vulnerable population group (McAnulty et al., 2009). Another documented reason for the improvement in developmental areas for premature infants having received an EI programme is further structural change. A study investigating the neurophysiology and neurostructure of premature infants' brains following EI was conducted on 30 infants ranging between 27 and 33 weeks gestation. This study showed that following an EI programme there had been pruning of over-connections which was postulated to aid in allowing the neurodevelopmental processing to be easier for the infants to achieve (Als et al., 2012). It also showed an significant decrease in the unmyelinated white matter and increased cortical grey matter when compared to infants who had not received any EI programme (Als et al., 2012). The common techniques that the Als study have with the current programme is that of positioning and massage.

Contrary to the other research done a systematic review was conducted on the effectiveness of NIDCAP. This review included 627 premature infants who received the NIDCAP programme did not find any significant improvement in long-term neurodevelopmental outcomes (Ohlsson and Jacobs, 2013). This study once again had the positioning and massage in common but not the passive movements and joint compressions. A smaller review conducted on 38 ELBW infants who were followed up for eight years showed a significant improvement following early intervention in the areas of neuropsychology and neurophysiology (McAnulty et al., 2009). The differences in these studies could be attributed to the gestational ages of their sample sizes. The McAnulty review included infants born earlier than 29 weeks, whereas the Ohlsson and Jacobs study included premature infants of varying gestational ages (Ohlsson and Jacobs, 2013; Cristofalo et al., 2013; McAnulty et al., 2009).

6.11 Conclusion

This study has shown that the combination of passive movements, joint compressions, massage and positioning have a significant effect on all three developmental domains that were tested at the testing ages. The regression analysis for all the developmental domains show that the treatment was a factor predictive of improved developmental

outcome. In the motor developmental domain, for the experimental group the factors predictive of outcome were treatment, gestation and IVH. The control group, factors were gestational and NEC. In the language developmental domain, the factors predictive of outcome for the experimental group were treatment and surfactant usage. The only factor in the control group was that of surfactant usage. In the cognitive developmental domain, the factors predicative of outcome in the experimental group were treatment, surfactant usage and gestation. In the control group, the factors were gestation and surfactant usage. This study has shown that this EI programme can make a significant difference to the developmental domains of this at-risk population group.

6.12 Limitations of the study

- The use of the modified nominal group technique for the panel discussion study design does not allow for many stakeholders to give their input.
- Two hospitals were used for different sample groups to decrease ethical concerns of withholding treatment. Differences in medical management between the two units could be a factor that influences the results of the study. The potential bias relating to the differences in the two units is a significant limitation of this study. This can also lead to the risk of selection bias.
- There is not enough evidence for the standardisation of care for the control unit.
- The study location and hospital choice were that of a higher socioeconomic population group. This could lead to a bias in the results.
- Only the majority of feed was documented by NICU staff. For this reason, there cannot be a more detailed investigation into this area and its role in development.
- No maternal education and socio-economic details were obtained from the caregivers.
- Management of the infants' post discharge was not standardised. The impact of home environment and parental practices as well as out-patient rehabilitation could be important confounding factors in this study.
- Infants that required intervention were still included in the study. Their data may have caused results to include improved results that were due to the post-

discharge intervention rather than that study intervention. However, this would affect the results of both groups equally.

6.13 Implications for the study

The results of this study have shown that a programme consisting of massage, joint compression and nesting is a developmentally effective programme that can be implemented in NICUs to improve the different developmental areas of premature infants.

6.14 Recommendations based on the study

This early intervention programme is easy to administer and the only cost being that of the training of the therapists who administer the programme in NICUs. This could be in-service training given by an experienced paediatric physiotherapist. This programme may also be taught to parents in under-resourced settings allowing for improved maternal-infant bonding which would benefit both mother and infant.

6.15 Recommendations for future research

- A consensus panel from more than one region can be done to ensure that opinions from more experts in their parts of the country are taken into account. This will allow the study to be more representative of the general South African neonatal population.
- Further research into the programme being implemented in the under-resourced public setting can be conducted to assess whether it is feasible to implement in the public setting.
- The length of follow up could be increased to see whether there are any extended benefits past the 18-month age that this study looked into.
- The possible link between long term cognitive development due to early motor development based on this programme should be looked into as seen in other studies (Piek et al., 2008).
- A change over time statistical analysis can be done using a larger sample size
- This study could be repeated with greater parental involvement to further study whether the results of allowing parents and caregivers to be involved in the developmental care of their infants, which has been shown to further improve

developmental outcomes (Shields, 2016). The possibility of KMC being added to the programme in a structured and standardised manner should also be investigated as this is a widely used technique in public settings.

- The impact of developmental intervention on parenting stress, maternal education and parental Health-related quality of life (HRQoL) should be investigated.

The conclusions drawn from this study are presented in chapter seven.

Chapter 7: CONCLUSION

The aim of this study was to develop and assess the effect of a NICU developmental programme on the developmental outcomes of premature infants at six, 12 and 18 months. The programme was developed based on an expert panel discussion and was implemented in the NICU on a subject group of 70 premature infants. The 70-subject control group was sourced from a neighbouring NICU who received all the same treatment protocols except the EI programme. The subjects were then assessed at six-, 12- and 18-months using the BSID III.

The findings of this study support the use of this programme as an EI programme to help these at-risk infants as the results show that the risk of the known developmental delay that can affect premature infants, is reduced. The developmental area with the greatest impact was that of motor development, both in the gross and fine motor development areas. The regression analysis showed how in all three developmental domains the treatment given was a predictive factor of the developmental outcomes.

This study shows how sensory-motor modalities can have an impact on all other developmental systems causing positive change. The results of this study show how physiotherapy can have a positive impact on premature infants and can assist in decreasing the burden of disease on the population by ensuring this population group is given optimal developmental care during an important time of brain plasticity allowing for improved developmental outcome.

The findings in this study support numerous other studies done globally. The results of this study show are important as the programme can be implemented into various hospital NICUs with physiotherapists to aid in the improvement of the morbidity of this population group.

BIBLIOGRAPHY

CanChild Resources. Gross Motor Function Classification System - Expanded & Revised (GMFCS - E & R). Available at https://canchild.ca/en/resources/42-gross-motor-function-classification-system-expanded-revised-gmfcs-e-r. Accessed 8 Aug 2015.

ABDALLAH, B., BADR, L. K. & HAWWARI, M. 2013. The efficacy of massage on short and long term outcomes in preterm infants. *Infant Behavior and Development,* 36**,** 662-669.

ABDEL-HADY, H., SHOUMAN, B. & ALY, H. 2011. Early weaning from CPAP to high flow nasal cannula in preterm infants is associated with prolonged oxygen requirement: A randomized controlled trial. *Early Human Development,* 87**,** 205-208.

ACKERMANN, H., MATHIAK, K. & RIECKER, A. 2007. The contribution of the cerebellum to speech production and speech perception: Clinical and functional imaging data. *The Cerebellum,* 6**,** 202 - 213.

AKKOYUN, I., OTO, S., YILMAZ, G., GURAKAN, B., TARCAN, A., ANUK, D., AKGUN, S. & AKOVA, Y. A. 2006. Risk Factors in the Development of Mild and Severe Retinopathy of Prematurity. *Journal of American Association for Pediatric Ophthalmology and Strabismus,* 10**,** 449-453.

ALBERS, C. A. & GRIEVE, A. J. 2007. Test Review: Bayley, N. (2006). Bayley Scales of Infant and Toddler Development– Third Edition. San Antonio, TX: Harcourt Assessment. *Journal of Psychoeducational Assessment,* 25**,** 180-190.

ALCOCK, K. 2006. The development of oral motor control and language. *Down Syndrome Research and Practice,* 11**,** 1 - 8.

ALCOCK, K. J. & KRAWCZYK, K. 2010. Individual differences in language development: relationship with motor skill at 21 months. *Developmental Science,* 13**,** 677-691.

ALIABADI, F. & ASKARY, R. K. 2013. Effects of tactile-kinesthetic stimulation on low birth weight neonates. *Iranian journal of pediatrics,* 23**,** 289-294.

ALLEN, K. A. 2012. Promoting and protecting infant sleep. *Advances in neonatal care : official journal of the National Association of Neonatal Nurses,* 12**,** 288-291.

ALLEN, M. 2008. Neurodevelopmental outcomes of preterm infants. *Current Opinions in Neurology,* 21**,** 123 - 128.

ALLIEVI, A. G., ARICHI, T., TUSOR, N., KIMPTON, J., ARULKUMARAN, S., COUNSELL, S. J., EDWARDS, A. D. & BURDET, E. 2016. Maturation of Sensori-Motor Functional Responses in the Preterm Brain. *Cerebral Cortex,* 26**,** 402–413.

ALLIN, M., NOSARTI, C., NARBERHAUS, A., WALSHE, M., FREARSON, S., KALPAKIDOU, A., WYATT, J., RIFKIN, L. & MURRAY, R. 2007. Growth of the Corpus Callosum in Adolescents Born Preterm. *Archives of Pediatric & Adolescent Medicine,* 161**,** 1183 - 1189.

ALLRED EN, C. A., FRAIOLI A, DAMMANN O, DROSTE P, DUKER J,GISE R, KUBAN K, LEVITON A, O'SHEA M, PANETH N, PETERSEN R, TRESE M, STOESSEL K, VANDERVEEN D, WALLACE D, WEAVER G 2014. Retinopathy of prematurity and brain damage in the very preterm newborn. *Journal of AAPOS,* 18**,** 241 - 247.

ALS, H. 1986. Program Guide - Newborn Individualized Developmental Care and Assessment Program (NIDCAP): An education and training program for health care professionals *In:* CORPORATION, B. C. S. M. C. (ed.).

ALS, H., DUFFY, F. H., MCANULTY, G., BUTLER, S. C., LIGHTBODY, L., KOSTA, S., WEISENFELD, N. I., ROBERTSON, R., PARAD, R. B., RINGER, S. A., BLICKMAN, J. G., ZURAKOWSKI, D. & WARFIELD, S. K. 2012. NIDCAP

improves brain function and structure in preterm infants with severe intrauterine growth restriction. *Journal Of Perinatology,* 32**,** 797.
ALS, H., DUFFY, F. H., MCANULTY, G. B., RIVKIN, M. J., VAJAPEYAM, S., MULKERN, R. V., WARFIELD, S. K., HUPPI, P. S., BUTLER, S. C., CONNEMAN, N., FISCHER, C. & EICHENWALD, E. C. 2004. Early experience alters brain function and structure. *Pediatrics,* 113**,** 846-857.
ALTIMIER, L. & PHILLIPS, R. 2016. The Neonatal Integrative Developmental Care Model: Advanced Clinical Applications of the Seven Core Measures for Neuroprotective Family-centered Developmental Care. *Newborn and Infant Nursing Reviews,* 16**,** 230-244.
ÁLVAREZ, M. J., FERNÁNDEZ, D., GÓMEZ-SALGADO, J., RODRÍGUEZ-GONZÁLEZ, D., ROSÓN, M. & LAPEÑA, S. 2017. The effects of massage therapy in hospitalized preterm neonates: A systematic review. *International Journal of Nursing Studies,* 69**,** 119-136.
ANDERSON, D. E. & PATEL, A. D. 2018. Infants born preterm, stress, and neurodevelopment in the neonatal intensive care unit: might music have an impact? *Developmental Medicine & Child Neurology,* 60**,** 256-266.
ANDERSON, P. J., DE LUCA, C. R. & HUTCHINSON, E. E. A. 2010. Underestimation of Developmental Delay by the New Bayley-III Scale. *Archives of Pediatric & Adolescent Medicine,* 164**,** 352-356.
ANDERSON, P. J. & DOYLE, L. W. 2008. Cognitive and Educational Deficits in Children Born Extremely Preterm. *Semin Perinatol,* 32**,** 51- 58.
ARDIEL, E. & RANKIN, C. 2010. The importance of touch in development. *Paediatrics & Child Health,* 15**,** 153–156.
ARICHI, T., MORAUX, A., MELENDEZ, A., DORIA, V., GROPPO, M., MERCHANT, N., COMBS, S., BURDET, E., LARKMAN, D. J., COUNSELL, S. J., BECKMANN, C. F. & EDWARDS, A. D. 2010. Somatosensory cortical activation identified by functional MRI in preterm and term infants. *NeuroImage,* 49**,** 2063-2071.
ASADOLLAHI, M., JABRAEILI, M., MAHALLEI, M., ASGARI JAFARABADI, M. & EBRAHIMI, S. 2016. Effects of Gentle Human Touch and Field Massage on Urine Cortisol Level in Premature Infants: A Randomized, Controlled Clinical Trial. *Journal of Caring Sciences,* 5**,** 187-194.
ASKIE, L. M., HENDERSON-SMART, D. J., IRWIG, L. & SIMPSON, J. M. 2003. Oxygen-Saturation Targets and Outcomes in Extremely Preterm Infants. *New England Journal of Medicine,* 349**,** 959-967.
ASSAIANTE, C., MALLAU, S., VIEL, S., JOVER, M. & SCHMITZ, C. 2005. Development of Postural Control in Healthy Children: A Functional Approach. *Neural Plasticity,* 12.
AUGUST, D. L., EDMONDS, L., BROWN, D. K., MURPHY, M. & KANDASAMY, Y. 2014. Pressure injuries to the skin in a neonatal unit: Fact or fiction. *Journal of Neonatal Nursing,* 20**,** 129-137.
AYLWARD, G. P. 2014. Neurodevelopmental Outcomes of Infants Born Prematurely. *Journal of Developmental & Behavioral Pediatrics,* 35**,** 394-407.
AZARMNEJAD, E., SARHANGI, F., JAVADI, M. & REJEH, N. 2015. The Effect of Mother's Voice on Arterial Blood Sampling Induced Pain in Neonates Hospitalized in Neonate Intensive Care Unit. *Global Journal of Health Science,* 7**,** 198-204.
BACK, S. A. & MILLER, S. P. 2014. Brain injury in premature neonates: A primary cerebral dysmaturation disorder? *Annals of Neurology,* 75**,** 469-486.

BADR, L. K., ABDALLAH, B. & KAHALE, L. 2015. A Meta-Analysis of Preterm Infant Massage: An Ancient Practice With Contemporary Applications. *MCN Am J Matern Child Nurs,* 40.

BAILEY, P. J. & SNOWLING, M. J. 2002. Auditory processing and the development of language and literacy. *British Medical Bulletin,* 63**,** 135-146.

BALL, G., BOARDMAN, J. P., RUECKERT, D., ALJABAR, P., ARICHI, T., MERCHANT, N., GOUSIAS, I. S., EDWARDS, A. D. & COUNSELL, S. J. 2012. The Effect of Preterm Birth on Thalamic and Cortical Development. *Cerebral Cortex (New York, NY),* 22**,** 1016-1024.

BALLABH, P. 2010. Intraventricular Hemorrhage in Premature Infants: Mechanism of Disease. *Pediatr Res,* 67**,** 1-8.

BALLANTYNE, M., BENZIES, K. M., MCDONALD, S., MAGILL-EVANS, J. & TOUGH, S. 2016. Risk of developmental delay: Comparison of late preterm and full term Canadian infants at age 12 months. *Early Human Development,* 101**,** 27-32.

BALLARD, J. L., KHOURY, J. C., WEDIG, K., WANG, L., EILERS-WALSMAN, B. L. & LIPP, R. 1991. New Ballard Score, expanded to include extremely premature infants. *The Journal of Pediatrics,* 119**,** 417-423.

BALLOT, D. E., POTTERTON, J., CHIRWA, T., HILBURN, N. & COOPER, P. A. 2012. Developmental outcome of very low birth weight infants in a developing country. *BMC Pediatrics,* 12**,** 11.

BALLOT, D. E., RAMDIN, T., RAKOTSOANE, D., AGABA, F., DAVIES, V. A., CHIRWA, T. & COOPER, P. A. 2017. Use of the Bayley Scales of Infant and Toddler Development, Third Edition, to Assess Developmental Outcome in Infants and Young Children in an Urban Setting in South Africa. *International Scholarly Research Notices,* 2017**,** 1631760.

BARRADAS, J., FONSECA, A., GUIMARÃES, C. L. N. & LIMA, G. M. D. S. 2006. A relação entre posicionamento do prematuro no Método Mãe-Canguru e desenvolvimento neuropsicomotor precoce. *Jornal de Pediatria,* 82**,** 475-480.

BARROS, F. C., PAPAGEORGHIOU, A. T., VICTORA, C. G., NOBLE, J. A., PANG, R., IAMS, J., CHEIKH ISMAIL, L., GOLDENBERG, R. L., LAMBERT, A., KRAMER, M. S., CARVALHO, M., CONDE-AGUDELO, A., JAFFER, Y. A., BERTINO, E., GRAVETT, M. G., ALTMAN, D. G., OHUMA, E. O., PURWAR, M., FREDERICK, I. O., BHUTTA, Z. A., KENNEDY, S. H. & VILLAR, J. 2015. The Distribution of Clinical Phenotypes of Preterm Birth Syndrome: Implications for Prevention. *JAMA Pediatrics,* 169**,** 220-229.

BARTOK, C. J. 2010. Babies Fed Breastmilk by Breast Versus by Bottle: A Pilot Study Evaluating Early Growth Patterns. *Breastfeeding Medicine,* 6**,** 117-124.

BARTON, E. E., REICHOW, B., SCHNITZ, A., SMITH, I. C. & SHERLOCK, D. 2015. A systematic review of sensory-based treatments for children with disabilities. *Research in Developmental Disabilities,* 37**,** 64-80.

BASIRI-MOGHADAM, M., BASIRI-MOGHADAM, K., KIANMEHR, M. & JANI, S. 2015. The effect of massage on neonatal jaundice in stable preterm newborn infants: a randomized controlled trial. *J Pak Med Assoc,* 65.

BASSAN, H., LIMPEROPOULOS, C., VISCONTI, K., MAYER, D. L., FELDMAN, H. A., AVERY, L., BENSON, C. B., STEWART, J., RINGER, S. A., SOUL, J. S., VOLPE, J. J. & DU PLESSIS, A. J. 2007. Neurodevelopmental outcome in survivors of periventricular hemorrhagic infarction. *Pediatrics,* 120**,** 785-92.

BAYLEY, N. 2006. *Bayley Scales of Infant and Toddler Development Third Edition Technical Manual,* Bloomington, Pearson.

BECK, S., WOJDYLA, D., SAY, L., BETRAN, A. P., MERIALDI, M., REQUEJO, J. H., RUBENS, C., MENON, R. & VAN LOOK, P. F. 2010. The worldwide incidence of preterm birth: a systematic review of maternal mortality and morbidity. *Bull World Health Organ,* 88**,** 31-8.

BEKER, F., OPIE, G., NOBLE, E., JIANG, Y. & BLOOMFIELD, F. H. 2017. Smell and Taste to Improve Nutrition in Very Preterm Infants: A Randomized Controlled Pilot Trial. *Neonatology,* 111**,** 260-266.

BELFORT, M. B., ANDERSON, P. J., NOWAK, V. A., LEE, K. J., MOLESWORTH, C., THOMPSON, D. K., DOYLE, L. W. & INDER, T. E. 2016. Breast Milk Feeding, Brain Development, and Neurocognitive Outcomes: A 7-Year Longitudinal Study in Infants Born at Less Than 30 Weeks' Gestation. *The Journal of Pediatrics*.

BELSKY, J. & DE HAAN, M. 2011. Annual Research Review: Parenting and children's brain development: the end of the beginning. *Journal of Child Psychology and Psychiatry,* 52**,** 409-428.

BEN-YEHUDAH, G., GUEDICHE, S. & FIEZ, J. A. 2007. Cerebellar contributions to verbal working memory: beyond cognitive theory. *The Cerebellum,* 6**,** 193 - 120.

BENARROCH, E. E. 2012. Insulin-like growth factors in the brain and their potential clinical implications. *Neurology,* 79**,** 2148.

BENZIES, K. M., MAGILL-EVANS, J. E., HAYDEN, K. A. & BALLANTYNE, M. 2013. Key components of early intervention programs for preterm infants and their parents: a systematic review and meta-analysis. *BMC Pregnancy and Childbirth,* 13**,** S10.

BERGER, R. & SÖDER, S. 2015. Neuroprotection in Preterm Infants. *BioMed Research International,* 2015**,** 257139.

BERNSHTEIN, N. A. 1967. The co-ordination and regulation of movements.

BIAGIONI, E., FRISONE, M. F., LAROCHE, S., KAPETANAKIS, B. A., RICCI, D., ADEYI-OBE, M., LEWIS, H., KENNEA, N., CIONI, G., COWAN, F., RUTHERFORD, M., AZZOPARDI, D. & MERCURI, E. 2007. Maturation of cerebral electrical activity and development of cortical folding in young very preterm infants. *Clin Neurophysiol,* 118**,** 53-9.

BICKLE GRAZ, M., TOLSA, J.-F. & FISCHER FUMEAUX, C. J. 2015. Being Small for Gestational Age: Does it Matter for the Neurodevelopment of Premature Infants? A Cohort Study. *PLoS ONE,* 10**,** e0125769.

BIELENINIK, Ł. & GOLD, C. 2014. EARLY INTERVENTION FOR PREMATURE INFANTS IN NEONATAL INTENSIVE CARE UNIT. *Acta Neuropsychologica,* 12**,** 185-203.

BJÖRN, P. M., KAKKURI, I., KARVONEN, P. & LEPPÄNEN, P. H. T. 2012. Accelerating early language development with multi-sensory training. *Early Child Development and Care,* 182**,** 435-451.

BLAIR, C. 2010. Stress and the Development of Self-Regulation in Context. *Child Development Perspectives,* 4**,** 181-188.

BLAUW-HOSPERS, C. H., DE GRAAF-PETERS, V. B., DIRKS, T., BOS, A. F. & HADDERS-ALGRA, M. 2007. Does early intervention in infants at high risk for a developmental motor disorder improve motor and cognitive development? *Neuroscience & Biobehavioral Reviews,* 31**,** 1201-1212.

BLENCOWE, H., COUSENS, S., CHOU, D., OESTERGAARD, M., SAY, L., MOLLER, A.-B., KINNEY, M., LAWN, J. & THE BORN TOO SOON PRETERM BIRTH ACTION, G. 2013a. Born Too Soon: The global epidemiology of 15 million preterm births. *Reproductive Health,* 10**,** S2.

BLENCOWE, H., LEE, A. C., COUSENS, S., BAHALIM, A., NARWAL, R., ZHONG, N., CHOU, D., SAY, L., MODI, N. & KATZ, J. 2013b. Preterm birth-associated

neurodevelopmental impairment estimates at regional and global levels for 2010. *Pediatr Res,* 74.
BOLISETTY, S., DHAWAN, A., ABDEL-LATIF, M., BAJUK, B., STACK, J. & K., L. 2014. Intraventricular Hemorrhage and Neurodevelopmental Outcomes in Extreme Preterm Infants. *Pediatrics,* 133**,** 55 - 62.
BOONYONG, S., SIU, K.-C., VAN DONKELAAR, P., CHOU, L.-S. & WOOLLACOTT, M. H. 2012. Development of postural control during gait in typically developing children: The effects of dual-task conditions. *Gait & Posture,* 35**,** 428-434.
BORONAT, N., AGUAR, M., ROOK, D., IRIONDO, M., BRUGADA, M., CERNADA, M., NUÑEZ, A., IZQUIERDO, M., CUBELLS, E., MARTINEZ, M., PARRA, A., VAN GOUDOEVER, H. & VENTO, M. 2016. Survival and Neurodevelopmental Outcomes of Preterms Resuscitated With Different Oxygen Fractions. *Pediatrics,* 138.
BOSCH, K., GERSS, J. & ROSENBAUM, D. 2010. Development of healthy children's feet--nine-year results of a longitudinal investigation of plantar loading patterns. *Gait Posture,* 32**,** 564-71.
BRADDICK, O. & ATKINSON, J. 2011. Development of human visual function. *Vision Research,* 51**,** 1588-1609.
BREEMAN, L. D., JAEKEL, J., BAUMANN, N., BARTMANN, P. & WOLKE, D. 2017. Neonatal predictors of cognitive ability in adults born very preterm: a prospective cohort study. *Developmental Medicine & Child Neurology***,** n/a-n/a.
BRITS, H., ADRIAANSE, M., RALL, D. M., VAN BILJON, M., VAN DER WALT, A. & JOUBERT, G. 2015. Causes of prematurity in the Bloemfontein Academic Complex. *South African Family Practice,* 57**,** 223-226.
BRÖRING, T., OOSTROM, K. J., LAFEBER, H. N., JANSMA, E. P. & OOSTERLAAN, J. 2017. Sensory modulation in preterm children: Theoretical perspective and systematic review. *PLOS ONE,* 12**,** e0170828.
BRUDERER, A. G., DANIELSON, D. K., KANDHADAI, P. & WERKER, J. F. 2015. Sensorimotor influences on speech perception in infancy. *Proceedings of the National Academy of Sciences,* 112**,** 13531.
BRUMMELTE, S., GRUNAU, R. E., CHAU, V., POSKITT, K. J., BRANT, R., VINALL, J., GOVER, A., SYNNES, A. R. & MILLER, S. P. 2012. Procedural pain and brain development in premature newborns. *Annals of Neurology,* 71**,** 385-396.
BUCHER, H., KILLER, C., OCHSNER, Y., VAIHINGER, S. & FAUCHÈRE, J.-C. 2002. Growth, developmental milestones and health problems in the first 2 years in very preterm infants compared with term infants: a population based study. *European Journal of Pediatrics,* 161**,** 151-156.
BUDDHAVARAPU, S., MANICKARAJ, S., LODHA, A. & SORAISHAM, A. S. 2015. Does High Protein Intake During First Week of Life Improve Growth and Neurodevelopmental Outcome at 18 months Corrected Age in Extremely Preterm Infants? *Indian J Pediatr*.
BUSS, C., ENTRINGER, S., SWANSON, J. M. & WADHWA, P. D. 2012. The Role of Stress in Brain Development: The Gestational Environment's Long-Term Effects on the Brain. *Cerebrum: the Dana Forum on Brain Science,* 2012**,** 4.
BYRNE, E. & CAMPBELL, S. K. 2013. Physical therapy observation and assessment in the neonatal intensive care unit. *Phys Occup Ther Pediatr,* 33**,** 39-74.
BYRNE E, G. J. 2013. Physical Therapy Intervention in the Neonatal Intensive Care Unit. *Physical & Occupational Therapy in Pediatrics,* 33**,** 75-110.

CABRAL, T. I., PEREIRA DA SILVA, L. G., TUDELLA, E. & SIMÕES MARTINEZ, C. M. 2015. Motor development and sensory processing: A comparative study between preterm and term infants. *Research in Developmental Disabilities,* 36**,** 102-107.

CAESAR, R., BOYD, R. N., COLDITZ, P., CIONI, G., WARE, R. S., SALTHOUSE, K., DOHERTY, J., JACKSON, M., MATTHEWS, L., HURLEY, T., MOROSINI, A., THOMAS, C., CAMADOO, L. & BAER, E. 2016. Early prediction of typical outcome and mild developmental delay for prioritisation of service delivery for very preterm and very low birthweight infants: a study protocol. *BMJ Open,* 6**,** e010726.

CAMPBELL, S., PALISANO, R. & ORLIN, M. 2011. *Campbell's Physical Therapy for Children Expert Consult, 4th Edition,* Missouri, Saunders.

CAMPBELL, S. K., ZAWACKI, L., RANKIN, K. M., YODER, J. C., SHAPIRO, N., LI, Z. & WHITE-TRAUT, R. 2013. Concurrent Validity of the TIMP and the Bayley III Scales at 6 Weeks Corrected Age. *Pediatric physical therapy : the official publication of the Section on Pediatrics of the American Physical Therapy Association,* 25**,** 395-401.

CÂNDIA, M. F., OSAKU, E. F., LEITE, M. A., TOCCOLINI, B., COSTA, N. L., TEIXEIRA, S. N., COSTA, C. R. L. D. M., PIANA, P. A., CRISTOVAM, M. A. D. S. & OSAKU, N. O. 2014. Influence of prone positioning on premature newborn infant stress assessed by means of salivary cortisol measurement: pilot study. *Revista Brasileira de Terapia Intensiva,* 26**,** 169-175.

CANO-DE-LA-CUERDA, R., MOLERO-SÁNCHEZ, A., CARRATALÁ-TEJADA, M., ALGUACIL-DIEGO, I. M., MOLINA-RUEDA, F., MIANGOLARRA-PAGE, J. C. & TORRICELLI, D. 2015. Theories and control models and motor learning: Clinical applications in neurorehabilitation. *Neurología (English Edition),* 30**,** 32-41.

CASARTELLI, L., FEDERICI, A., CESAREO, A., BIFFI, E., VALTORTA, G., MOLTENI, M., RONCONI, L. & BORGATTI, R. 2017. Role of the cerebellum in high stages of motor planning hierarchy. *Journal of Neurophysiology,* 117**,** 1474-1482.

CASCIO, C. J. 2010. Somatosensory processing in neurodevelopmental disorders. *Journal of Neurodevelopmental Disorders,* 2**,** 62-69.

CASTANYS-MUÑOZ, E., KENNEDY, K., CASTAÑEDA-GUTIÉRREZ, E., FORSYTH, S., GODFREY, K. M., KOLETZKO, B., OZANNE, S. E., RUEDA, R., SCHOEMAKER, M., VAN DER BEEK, E. M., VAN BUUREN, S. & ONG, K. K. 2017. Systematic review indicates postnatal growth in term infants born small-for-gestational-age being associated with later neurocognitive and metabolic outcomes. *Acta Paediatrica,* 106**,** 1230-1238.

CAUGHEY, A. B., ROBINSON, J. N. & NORWITZ, E. R. 2008. Contemporary diagnosis and management of preterm premature rupture of membranes. *Rev Obstet Gynecol,* 1**,** 11-22.

CAVALLARO, G., FILIPPI, L., BAGNOLI, P., LA MARCA, G., CRISTOFORI, G., RAFFAELI, G., PADRINI, L., ARAIMO, G., FUMAGALLI, M., GROPPO, M., DAL MONTE, M., OSNAGHI, S., FIORINI, P. & MOSCA, F. 2014. The pathophysiology of retinopathy of prematurity: an update of previous and recent knowledge. *Acta Ophthalmologica,* 92**,** 2-20.

CHAWANPAIBOON, S., VOGEL, J. P., MOLLER, A.-B., LUMBIGANON, P., PETZOLD, M., HOGAN, D., LANDOULSI, S., JAMPATHONG, N., KONGWATTANAKUL, K., LAOPAIBOON, M., LEWIS, C., RATTANAKANOKCHAI, S., TENG, D. N., THINKHAMROP, J., WATANANIRUN, K., ZHANG, J., ZHOU, W. & GÜLMEZOGLU, A. M. 2019. Global, regional, and national estimates of levels of preterm birth in 2014: a systematic review and modelling analysis. *The Lancet Global Health,* 7**,** e37-e46.

CHAWLA, S., NATARAJAN, G., SHANKARAN, S., PAPPAS, A., STOLL, B. J., CARLO, W. A., SAHA, S., DAS, A., LAPTOOK, A. R., HIGGINS, R. D., FOR THE NATIONAL INSTITUTE OF CHILD, H. & HUMAN DEVELOPMENT NEONATAL RESEARCH, N. 2016. Association of Neurodevelopmental Outcomes and Neonatal Morbidities of Extremely Premature Infants With Differential Exposure to Antenatal Steroids. *JAMA pediatrics,* 170**,** 1164-1172.

CHEN, M., ÇITIL, A., MCCABE, F., LEICHT, K. M., FIASCONE, J., DAMMANN, C. E. L. & DAMMANN, O. 2011. Infection, Oxygen, and Immaturity: Interacting Risk Factors for Retinopathy of Prematurity. *Neonatology,* 99**,** 125-132.

CHEN, S.-S., TZENG, Y.-L., GAU, B.-S., KUO, P.-C. & CHEN, J.-Y. 2013. Effects of prone and supine positioning on gastric residuals in preterm infants: A time series with cross-over study. *International Journal of Nursing Studies,* 50**,** 1459-1467.

CHEONG, J. L. & DOYLE, L. W. 2012. Increasing rates of prematurity and epidemiology of late preterm birth. *J Paediatr Child Health,* 48**,** 784-8.

CHOI, H., KIM, S.-J., OH, J., LEE, M.-N., KIM, S. & KANG, K.-A. 2015. The effects of massage therapy on physical growth and gastrointestinal function in premature infants. *Journal of Child Health Care,* 20**,** 394-404.

CHORNA, O., SOLOMON, J. E., SLAUGHTER, J. C. & STARK, A. R. M., N.L. 2014. Abnormal sensory reactivity in preterm infants during the first year correlates with adverse neurodevelopmental outcomes at 2 years of age. *Archives of Disease in Childhood.Fetal and Neonatal Edition,* 99.

CIONI, G., INGUAGGIATO, E. & SGANDURRA, G. 2016. Early intervention in neurodevelopmental disorders: underlying neural mechanisms. *Developmental Medicine & Child Neurology,* 58**,** 61-66.

CLARK, J. E. & METCALFE, J. S. 2002. The mountain of motor development: A metaphor.

CLOUCHOUX, C., KUDELSKI, D., GHOLIPOUR, A., WARFIELD, S. K., VISEUR, S., BOUYSSI-KOBAR, M., MARI, J.-L., EVANS, A. C., DU PLESSIS, A. J. & LIMPEROPOULOS, C. 2012. Quantitative in vivo MRI measurement of cortical development in the fetus. *Brain Structure and Function,* 217**,** 127-139.

COLETTI, M. F., CARAVALE, B., GASPARINI, C., FRANCO, F., CAMPI, F. & DOTTA, A. 2015. One-year neurodevelopmental outcome of very and late preterm infants: Risk factors and correlation with maternal stress. *Infant Behav Dev,* 39**,** 11-20.

CONDE- AGUDELO, A. & DÍAZ- ROSSELLO, J. L. 2016. Kangaroo mother care to reduce morbidity and mortality in low birthweight infants. *Cochrane Database of Systematic Reviews*.

CONG, X., WU, J., VITTNER, D., XU, W., HUSSAIN, N., GALVIN, S., FITZSIMONS, M., MCGRATH, J. M. & HENDERSON, W. A. 2017. The impact of cumulative pain/stress on neurobehavioral development of preterm infants in the NICU. *Early Human Development,* 108**,** 9-16.

CONNOLLY BH, O. M. N., GAITLAIN R 2012. Concurrent Validity of the Bayley-III and the Peabody Developmental Motor Scale–2. *Pediatric Physical Therapy,* 24**,** 345 - 352.

COUGHLIN, M., LOHMAN, M. B. & GIBBINS, S. 2010. Reliability and Effectiveness of an Infant Positioning Assessment Tool to Standardize Developmentally Supportive Positioning Practices in the Neonatal Intensive Care Unit. *Newborn and Infant Nursing Reviews,* 10**,** 104-106.

COUNSELL, S. J., SHEN, Y., BOARDMAN, J. P., LARKMAN, D. J., KAPELLOU, O., WARD, P., ALLSOP, J. M., COWAN, F. M., HAJNAL, J. V., EDWARDS, A. D. & RUTHERFORD, M. A. 2006. Axial and radial diffusivity in preterm infants who have

diffuse white matter changes on magnetic resonance imaging at term-equivalent age. *Pediatrics,* 117**,** 376-86.
CRISTOFALO, E. A., SCHANLER, R. J., BLANCO, C. L., SULLIVAN, S., TRAWOEGER, R., KIECHL-KOHLENDORFER, U., DUDELL, G., RECHTMAN, D. J., LEE, M. L., LUCAS, A. & ABRAMS, S. 2013. Randomized Trial of Exclusive Human Milk versus Preterm Formula Diets in Extremely Premature Infants. *The Journal of Pediatrics,* 163**,** 1592-1595.e1.
CULHANE, J. F., RAUH, V., MCCOLLUM, K. F., ELO, I. T. & HOGAN, V. 2002. Exposure to chronic stress and ethnic differences in rates of bacterial vaginosis among pregnant women. *American Journal of Obstetrics and Gynecology,* 187**,** 1272-1276.
CULLEN, K. E. 2012. The vestibular system: multimodal integration and encoding of self-motion for motor control. *Trends in Neurosciences,* 35**,** 185-196.
CURRIE, L., DODDS, L., SHEA, S., FLOWERDEW, G., MCLEAN, J., WALKER, R. & VINCER, M. 2012. Investigation of test characteristics of two screening tools in comparison with a gold standard assessment to detect developmental delay at 36 months: A pilot study. *Paediatrics & Child Health,* 17**,** 549-552.
DA COSTA RIBEIRO, C., ABRAMIDES, D. V. M., FUERTES, M. G., LOPES DOS SANTOS, P. N. & LAMÔNICA, D. A. C. 2016. Receptive language and intellectual abilities in preterm children. *Early Human Development,* 99**,** 57-60.
DAMMANN, O., BRINKHAUS, M. J., BARTELS, D. B., DORDELMANN, M., DRESSLER, F., KERK, J., DORK, T. & DAMMANN, C. E. 2009. Immaturity, perinatal inflammation, and retinopathy of prematurity: a multi-hit hypothesis. *Early Hum Dev,* 85**,** 325-9.
DAVIES JH, H. L. 2007. *Children in Intensive Care. A Survivial Guide,* London, Churchill Livingstone.
DAY, C. L. & RYAN, R. M. 2016. Bronchopulmonary dysplasia: new becomes old again! *Pediatric Research,* 81**,** 210.
DE GRAAF-PETERS, V. B. & HADDERS-ALGRA, M. 2006. Ontogeny of the human central nervous system: what is happening when? *Early Hum Dev,* 82**,** 257-66.
DE JESUS, L. C., PAPPAS, A., SHANKARAN, S., LI, L., DAS, A., BELL, E. F., STOLL, B. J., LAPTOOK, A. R., WALSH, M. C., HALE, E. C., NEWMAN, N. S., BARA, R. & HIGGINS, R. D. 2013. Outcomes of Small for Gestational Age Infants Born at <27 Weeks' Gestation. *The Journal of Pediatrics,* 163**,** 55-60.e3.
DE KIEVIET, J. F., PIEK, J. P., AARNOUDSE-MOENS, C. S. & OOSTERLAAN, J. 2009. Motor Development in Very Preterm and Very Low-Birth-Weight Children From Birth to Adolescence
A Meta-analysis. *JAMA,* 302**,** 2235 - 2242.
DE KIEVIET, J. F., ZOETEBIER, L., VAN ELBURG, R. M., VERMEULEN, R. J. & OOSTERLAAN, J. 2012. Brain development of very preterm and very low-birthweight children in childhood and adolescence: a meta-analysis. *Developmental Medicine & Child Neurology,* 54**,** 313-323.
DE ONIS, M. 2006. WHO Motor Development Study: Windows of achievement for six gross motor development milestones. *Acta Paediatrica. Supplement,* 95**,** 86-95.
DEONI, S. C. L., DEAN, D. C., PIRYATINSKY, I., O'MUIRCHEARTAIGH, J., WASKIEWICZ, N., LEHMAN, K., HAN, M. & DIRKS, H. 2013. Breastfeeding and early white matter development: A cross-sectional study. *NeuroImage,* 82**,** 77-86.
DEVELOPMENT, W. C. D. O. S. 2009. An Audit of Early Childhood Development facilities in the Western Cape, 2008 : final report. Cape Town : Department of Social Development, 2009. *In:* DEVELOPMENT, W. C. D. O. S. (ed.).

https://www.westerncape.gov.za/sites/www.westerncape.gov.za/files/documents/2010/6/ecd_quantitative_audit_2009.pdf.
DIEGO, M. A., FIELD, T. & HERNANDEZ-REIF, M. 2009. Procedural pain heart rate responses in massaged preterm infants. *Infant Behav Dev,* 32.
DIEGO, M. A., FIELD, T. & HERNANDEZ-REIF, M. 2014. Preterm infant weight gain is increased by massage therapy and exercise via different underlying mechanisms. *Early Hum Dev,* 90.
DODD, S. X. 2017. *Factors Influencing Fine and Gross Motor Development among Children 24 Months of Age: Results from the All Our Families Study.* Master of Science, University of Calgary.
DORN, F., WIRTH, L., GORBEY, S., WEGE, M., ZEMLIN, M., MAIER, R. F. & LEMMER, B. 2014. Influence of acoustic stimulation on the circadian and ultradian rhythm of premature infants. *Chronobiology International,* 31**,** 1062-1074.
DOS SANTOS MOTTA, M. M., FILHO, J. B. F., COBLENTZ, J. & FIOROT, C. A. 2011. Multiple pregnancies and its relationship with the development of retinopathy of prematurity (ROP). *Clinical Ophthalmology (Auckland, N.Z.),* 5**,** 1783-1787.
DOYLE, L. W., HALLIDAY, H. L., EHRENKRANZ, R. A., DAVIS, P. G. & SINCLAIR, J. C. 2005. Impact of Postnatal Systemic Corticosteroids on Mortality and Cerebral Palsy in Preterm Infants: Effect Modification by Risk for Chronic Lung Disease. *Pediatrics,* 115**,** 655.
DOYLE, L. W., HALLIDAY, H. L., EHRENKRANZ, R. A., DAVIS, P. G. & SINCLAIR, J. C. 2014. An Update on the Impact of Postnatal Systemic Corticosteroids on Mortality and Cerebral Palsy in Preterm Infants: Effect Modification by Risk of Bronchopulmonary Dysplasia. *The Journal of Pediatrics,* 165**,** 1258-1260.
DUBOIS, J., DEHAENE-LAMBERTZ, G., KULIKOVA, S., POUPON, C., HÜPPI, P. S. & HERTZ-PANNIER, L. 2014. The early development of brain white matter: A review of imaging studies in fetuses, newborns and infants. *Neuroscience,* 276**,** 48-71.
DUDEK-SHRIBER, L. E. O. T. R. L. & ZELAZNY, S. M. S. O. T. R. L. 2007. The Effects of Prone Positioning on the Quality and Acquisition of Developmental Milestones in Four-Month-Old Infants. *Pediatric Physical Therapy Spring,* 19**,** 48-55.
DUEKER, G., CHEN, J., COWLING, C. & HASKIN, B. 2016. Early developmental outcomes predicted by gestational age from 35 to 41 weeks. *Early Human Development,* 103**,** 85-90.
DUNCAN, A. F., BANN, C., BOATMAN, C., HINTZ, S. R., VAUCHER, Y. E., VOHR, B. R., YOLTON, K., HEYNE, R. J., THE EUNICE KENNEDY SHRIVER NATIONAL INSTITUTE OF CHILD, H. & HUMAN DEVELOPMENT NEONATAL RESEARCH, N. 2015. Do currently recommended Bayley III cutoffs overestimate motor impairment in infants born <27 weeks gestation? *Journal of perinatology : official journal of the California Perinatal Association,* 35**,** 516-521.
DUSING, S. C. & HARBOURNE, R. T. 2010. Variability in Postural Control During Infancy: Implications for Development, Assessment, and Intervention. *Physical Therapy,* 90**,** 1838-1849.
DUSING, S. C., LOBO, M. A., LEE, H.-M. & GALLOWAY, J. C. 2013. Intervention in the First Weeks of Life for Infants Born Late Preterm: A Case Series. *Pediatric physical therapy : the official publication of the Section on Pediatrics of the American Physical Therapy Association,* 25**,** 194-203.
EDELMAN, G. 1989. *Neural Darwinism. The Theory of Neuronal Group Selection,* Oxford, Oxford University Press.

EINSPIELER, C., BOS, A. F., LIBERTUS, M. E. & MARSCHIK, P. B. 2016. The General Movement Assessment Helps Us to Identify Preterm Infants at Risk for Cognitive Dysfunction. *Frontiers in Psychology,* 7**,** 406.

EINSPIELER, C., MARSCHIK, P. B. & PRECHTL, H. F. R. 2008. Human motor behavior: Prenatal origin and early postnatal development. *Zeitschrift für Psychologie/Journal of Psychology,* 216**,** 147-153.

EL-DIB, M., MASSARO, A. N., BULAS, D. & ALY, H. 2010. Neuroimaging and neurodevelopmental outcome of premature infants. *Am J Perinatol,* 27.

ELFAYOMY, A. K. & ALMASRY, S. M. 2014. Effects of a single course versus repeated courses of antenatal corticosteroids on fetal growth, placental morphometry and the differential regulation of vascular endothelial growth factor. *Journal of Obstetrics and Gynaecology Research,* 40**,** 2135-2145.

ELIAKIM, A., DOLFIN, T., WEISS, E., SHAINKIN-KESTENBAUM, R. & LIS, M. 2002. The Effects of Exercise on Body Weight and Circulating Leptin in Premature Infants. *Journal of Perinatology,* 22**,** 550 - 554.

EVENSEN, K. A. I., SKRANES, J., BRUBAKK, A.-M. & VIK, T. 2009. Predictive value of early motor evaluation in preterm very low birth weight and term small for gestational age children. *Early Human Development,* 85**,** 511-518.

FAGHIH JOUIBARI, M., BARADARAN, N., SHAMS AMIRI, R., NEJAT, F. & EL KHASHAB, M. 2011. Huge hydrocephalus: definition, management, and complications. *Child's Nervous System,* 27**,** 95-100.

FEDEWA, A. L. & AHN, S. 2011. The Effects of Physical Activity and Physical Fitness on Children's Achievement and Cognitive Outcomes. *Research Quarterly for Exercise and Sport,* 82**,** 521-535.

FELDMAN, H. M., LEE, E. S., YEATMAN, J. D. & YEOM, K. W. 2012. Language and reading skills in school-aged children and adolescents born preterm are associated with white matter properties on diffusion tensor imaging. *Neuropsychologia,* 50**,** 3348-3362.

FELDMAN, R. & EIDELMAN, A. 1998. Intervention programs for premature infants: how and do they affect development? *Clinics in Perinatology,* 25**,** 613-626.

FELDMAN, R. & EIDELMAN, A. I. 2003. Direct and indirect effects of breast milk on the neurobehavioral and cognitive development of premature infants. *Developmental Psychobiology,* 43**,** 109-119.

FELDMAN, R., SINGER, M. & ZAGOORY, O. 2010. Touch attenuates infants' physiological reactivity to stress. *Developmental Science,* 13**,** 271-278.

FERRARI, F., BERTONCELLI, N., GALLO, C., ROVERSI, M. F., GUERRA, M. P., RANZI, A. & HADDERS-ALGRA, M. 2007. Posture and movement in healthy preterm infants in supine position in and outside the nest. *Archives of disease in childhood. Fetal and neonatal edition,* 92**,** F386-F390.

FERREIRA, A. M. & BERGAMASCO, N. H. P. 2010. Análise comportamental de recém-nascidos pré-termos incluídos em um programa de estimulação tátil-cinestésica durante a internação hospitalar. *Brazilian Journal of Physical Therapy,* 14**,** 141-148.

FERREIRA, R. C., MELLO, R. R. & SILVA, K. S. 2014. Neonatal sepsis as a risk factor for neurodevelopmental changes in preterm infants with very loq birth weight. *J Pediatr (Rio J),* 90.

FIELD, T., DIEGO, M. & HERNANDEZ-REIF, M. 2010. Preterm infant massage therapy research: A review. *Infant Behavior and Development,* 33**,** 115-124.

FIELD, T., DIEGO, M. & HERNANDEZ-REIF, M. 2011. Potential underlying mechanisms for greater weight gain in massaged preterm infants. *Infant Behavior and Development,* 34**,** 383-389.

FIELD, T., DIEGO, M. A., HERNANDEZ-REIF, M., DEEDS, O. & FIGUEREIDO, B. 2006. Moderate versus light pressure massage therapy leads to greater weight gain in preterm infants. *Infant Behavior and Development,* 29**,** 574-578.
FIGLIO, D. N. P., GURYAN, J. P., KARBOWNIK, K. P. & ROTH, J. P. 2016. Long-term Cognitive and Health Outcomes of School-Aged Children Who Were Born Late-Term vs Full-Term. *JAMA Pediatrics,* 170**,** 758-764.
FITTS, P. M. & POSNER, M. I. 1967. *Human Movement,* Oxford, England, Brooks/Cole.
FLANNERY, D. D., O'DONNELL, E., KORNHAUSER, M., DYSART, K., GREENSPAN, J. & AGHAI, Z. H. 2016. Continuous Positive Airway Pressure versus Mechanical Ventilation on the Fist Day of Life in Very Low-Birth-Weight Infants. *American journal of perinatology,* 33**,** 939-944.
FLAVELL, J. H. 1999. Cognitive development: Children's knowledge about the mind. *Annual Review of Psychology,* 50**,** 21.
FOSTER, S. & VERNY, T. R. 2007a. The Development of Sensory Systems during the Prenatal Period. *Journal of Prenatal & Perinatal Psychology & Health,* 21**,** 271-280.
FOSTER, S. M. M. S. O. T. R. L. & VERNY, T. R. M. D. D. H. D. L. F. 2007b. The Development of Sensory Systems During the Prenatal Period. *Journal of Prenatal & Perinatal Psychology & Health,* 21**,** 271-280.
FOX, S. E., LEVITT, P. & NELSON III, C. A. 2010. How the Timing and Quality of Early Experiences Influence the Development of Brain Architecture. *Child Development,* 81**,** 28-40.
FREY, H. A. & KLEBANOFF, M. A. 2016. The epidemiology, etiology, and costs of preterm birth. *Seminars in Fetal and Neonatal Medicine,* 21**,** 68-73.
FRIEDERICI, A. D. 2011. The Brain Basis of Language Processing: From Structure to Function. *Physiological Reviews,* 91**,** 1357-1392.
FU, M. & ZUO, Y. 2011. Experience-dependent structural plasticity in the cortex. *Trends in Neurosciences,* 34**,** 177-187.
FUTAGI, Y., TORIBE, Y. & SUZUKI, Y. 2012. The Grasp Reflex and Moro Reflex in Infants: Hierarchy of Primitive Reflex Responses. *International Journal of Pediatrics,* 2012**,** 191562.
GABIS, L. V., HACHAM-PILOSOF, K., YOSEF, O. B., RABINOVITZ, G., LESHEM, G., SHILON-HADASS, A., BIRAN, Y., REICHMAN, B., KUINT, J. & BART, O. 2015. The Influence of a Multisensory Intervention for Preterm Infants Provided by Parents, on Developmental Abilities and on Parental Stress Levels. *Journal of Child Neurology,* 30**,** 896-903.
GAERLAN, M. G., ALPERT, P. T., CROSS, C., LOUIS, M. & KOWALSKI, S. 2012. Postural balance in young adults: The role of visual, vestibular and somatosensory systems. *Journal of the American Academy of Nurse Practitioners,* 24**,** 375-381.
GALINSKY, R., POLGLASE, G. R., HOOPER, S. B., BLACK, M. J. & MOSS, T. J. M. 2013. The Consequences of Chorioamnionitis: Preterm Birth and Effects on Development. *Journal of Pregnancy,* 2013**,** 11.
GALLAHUE, D. & OZMUN, J. 2006. *Understanding Motor Development: Infants, Children, Adolescents, Adults,* New York, McGraw-Hill International Edition.
GENTILE, J. R., RODEN, A. H. & KLEIN, R. D. 1972. An analysis-of-variance model for the intrasubject replication design. *Journal of Applied Behavior Analysis,* 5**,** 193-198.
GEORGE, J. M., BOYD, R. N., COLDITZ, P. B., ROSE, S. E., PANNEK, K., FRIPP, J., LINGWOOD, B. E., LAI, M. M., KONG, A. H. T., WARE, R. S., COULTHARD, A., FINN, C. M. & BANDARANAYAKE, S. E. 2015. PPREMO: a prospective cohort study of preterm infant brain structure and function to predict neurodevelopmental outcome. *BMC Pediatrics,* 15**,** 123.

GIRARD, N., CONFORT-GOUNY, S., SCHNEIDER, J., BARBERET, M., CHAPON, F., VIOLA, A., PINEAU, S., COMBAZ, X. & COZZONE, P. 2007. MR imaging of brain maturation. *J Neuroradiol,* 34**,** 290-310.

GIRARD, N. J., DORY-LAUTREC, P., KOOB, M. & DEDIU, A. M. 2012. MRI assessment of neonatal brain maturation. *Imaging,* 4**,** 613-632.

GLASS, H. C., COSTARINO, A. T., STAYER, S. A., BRETT, C., CLADIS, F. & DAVIS, P. J. 2015. Outcomes for Extremely Premature Infants. *Anesthesia and analgesia,* 120**,** 1337-1351.

GLASS, T. J. A., CHAU, V., GARDINER, J., FOONG, J., VINALL, J., ZWICKER, J. G., GRUNAU, R. E., SYNNES, A., POSKITT, K. J. & MILLER, S. P. 2017. Severe retinopathy of prematurity predicts delayed white matter maturation and poorer neurodevelopment. *Archives of Disease in Childhood - Fetal and Neonatal Edition,* 102**,** F532.

GOEL, K. M. & GUPTA, D. K. 2012. *Hutchison's Paediatrics,* JAYPEE BROTHERS MEDICAL PUBLISHERS (P) LTD.

GOLDENBERG, R. L., CULHANE, J. F., IAMS, J. D. & ROMERO, R. 2008. Epidemiology and causes of preterm birth. *The Lancet,* 371**,** 75-84.

GÖPEL, W., KRIBS, A., HÄRTEL, C., AVENARIUS, S., TEIG, N., GRONECK, P., OLBERTZ, D., ROLL, C., VOCHEM, M., WELLER, U., VON DER WENSE, A., WIEG, C., WINTGENS, J., PREUSS, M., ZIEGLER, A., ROTH, B., HERTING, E. & FOR THE GERMAN NEONATAL, N. 2015. Less invasive surfactant administration is associated with improved pulmonary outcomes in spontaneously breathing preterm infants. *Acta Paediatrica,* 104**,** 241-246.

GOUNA, G., RAKZA, T., KUISSI, E., PENNAFORTE, T., MUR, S. & STORME, L. 2013. Positioning Effects on Lung Function and Breathing Pattern in Premature Newborns. *The Journal of Pediatrics,* 162**,** 1133-1137.e1.

GOYEN, T. A. & LUI, K. 2002. Longitudinal motor development of "apparently normal" high-risk infants at 18 month, 3 years and 5 years. *Early Human Development,* 70**,** 103 - 115.

GRAVEN, S. N. & BROWNE, J. V. 2008a. Auditory Development in the Fetus and Infant. *Newborn and Infant Nursing Reviews,* 8**,** 187-193.

GRAVEN, S. N. & BROWNE, J. V. 2008b. Sensory Development in the Fetus, Neonate, and Infant: Introduction and Overview. *Newborn and Infant Nursing Reviews,* 8**,** 169-172.

GREENLEE, K. L. 2013. *Roles of Speech-Language Pathologists in the Neonatal Intensive Care Unit.* The University of Mississippi.

GRUNAU, R. E. 2013. Neonatal Pain in Very Preterm Infants: Long-Term Effects on Brain, Neurodevelopment and Pain Reactivity. *Rambam Maimonides Medical Journal,* 4**,** e0025.

GRUNAU, R. E., HOLSTI, L. & PETERS, J. W. B. 2006. Long-term consequences of pain in human neonates. *Seminars in Fetal and Neonatal Medicine,* 11**,** 268-275.

GUARINI, A., SANSAVINI, A., FABBRI, C., ALESSANDRONI, R., FALDELLA, G. & KARMILOFF-SMITH, A. 2009. Reconsidering the impact of preterm birth on language outcome. *Early Hum Dev,* 85**,** 639-45.

GUO, T. P., DUERDEN, E. G. P., ADAMS, E. M. D., CHAU, V. M. D., BRANSON, H. M. M., CHAKRAVARTY, M. M. P., POSKITT, K. J. M., SYNNES, A. M., GRUNAU, R. E. P. & MILLER, S. P. M. 2017. Quantitative assessment of white matter injury in preterm neonates: Association with outcomes. *Neurology,* 88**,** 614-622.

GUZZETTA, A., D'ACUNTO, M. G., CAROTENUTO, M., BERARDI, N., BANCALE, A. & BIAGIONI, E. 2011. The effects of preterm infant massage on brain electrical activity. *Dev Med Child Neurol,* 53.

HADDERS-ALGRA, M. 2010. Variation and Variability: Key Words in Human Motor Development. *Physical Therapy,* 90**,** 1823.
HADDERS-ALGRA, M. 2011. Challenges and limitations in early intervention. *Developmental Medicine & Child Neurology,* 53**,** 52-55.
HADDERS-ALGRA, M. 2018. Neural substrate and clinical significance of general movements: an update. *Developmental Medicine & Child Neurology,* 60**,** 39-46.
HADDERS-ALGRA, M. & PRECHTL, H. F. R. 1992. Developmental course of general movements in early infancy. I. Descriptive analysis of change in form. *Early Human Development,* 28**,** 201-213.
HARRISON, W. & GOODMAN, D. 2015. Epidemiologic Trends in Neonatal Intensive Care, 2007-2012. *JAMA Pediatr,* 169**,** 855-62.
HARTEMAN, J. C., GROENENDAAL, F., VAN HAASTERT, I. C., LIEM, K. D., STROINK, H., BIERINGS, M. B., HUISMAN, A. & DE VRIES, L. S. 2012. Atypical timing and presentation of periventricular haemorrhagic infarction in preterm infants: the role of thrombophilia. *Developmental Medicine & Child Neurology,* 54**,** 140-147.
HEDIGER, M. L., OVERPECK, M. D., RUAN, W. J. & TROENDLE, J. F. 2002. Birthweight and gestational age effects on motor and social development. *Paediatric and Perinatal Epidemiology,* 16**,** 33-46.
HELLSTRÖM, A., SMITH, L. E. H. & DAMMANN, O. 2013. Retinopathy of prematurity. *The Lancet,* 382**,** 1445-1457.
HERMANSEN, C. L. & MAHAJAN, A. 2015. Newborn Respiratory Distress. *American Family Physician,* 92**,** 994-1002.
HERNANDEZ-REIF, M., DIEGO, M. & FIELD, T. 2007. Preterm infants show reduced stress behaviors and activity after 5 days of massage therapy. *Infant Behav Dev,* 30.
HILDERMAN, C. G. E. & HARRIS, S. R. 2014. Early Intervention Post-Hospital Discharge for Infants Born Preterm. *Physical Therapy,* 94**,** 1211.
HILLMAN, N., KALLAPUR, S. G. & JOBE, A. 2012. Physiology of Transition from intrauterine to Extrauterine Life. *Clinics in perinatology,* 39**,** 769-783.
HILLMAN, S. J., STANSFIELD, B. W., RICHARDSON, A. M. & ROBB, J. E. 2009. Development of temporal and distance parameters of gait in normal children. *Gait & Posture,* 29**,** 81-85.
HINOJOSA-RODRÍGUEZ, M., HARMONY, T., CARRILLO-PRADO, C., VAN HORN, J. D., IRIMIA, A., TORGERSON, C. & JACOKES, Z. 2017. Clinical neuroimaging in the preterm infant: Diagnosis and prognosis. *NeuroImage : Clinical,* 16**,** 355-368.
HIRVONEN, M., OJALA, R., KORHONEN, P., HAATAJA, P., ERIKSSON, K., GISSLER, M., LUUKKAALA, T. & TAMMELA, O. 2014. Cerebral palsy among children born moderately and late preterm. *Pediatrics,* 134**,** e1584-93.
HO, Y. B., LEE, R. S., CHOW, C. B. & PANG, M. Y. 2010. Impact of massage therapy on motor outcomes in very low-birthweight infants: randomized controlled pilot study. *Pediatr Int,* 52.
HOEKSTRA, R. E., FERRARA, T. B., COUSER, R. J., PAYNE, N. R. & CONNETT, J. E. 2003. Survival and Long-Term Neurodevelopmental Outcome of Extremely Premature Infants Born at 23–26 Weeks' Gestational Age at a Tertiary Center. *Pediatrics,* 113**,** e1.
HOFMANN, W., SCHMEICHEL, B. J. & BADDELEY, A. D. 2012. Executive functions and self-regulation. *Trends in Cognitive Sciences,* 16**,** 174-180.
HORBAR, J. D. 1999. The Vermont Oxford Network: Evidence-Based Quality Improvement for Neonatology. *Pediatrics,* 103**,** 350.

HUGHES, A. J., REDSELL, S. A. & GLAZEBROOK, C. 2016. Motor Development Interventions for Preterm Infants: A Systematic Review and Meta-analysis. *Pediatrics,* 138.
HUNTER, C. J., UPPERMAN, J. S., FORD, H. R. & CAMERINI, V. 2008. Understanding the Susceptibility of the Premature Infant to Necrotizing Enterocolitis (NEC). *Pediatric Research,* 63**,** 117.
HUTCHEON, J. A., LISONKOVA, S. & JOSEPH, K. S. 2011. Epidemiology of pre-eclampsia and the other hypertensive disorders of pregnancy. *Best Practice & Research Clinical Obstetrics & Gynaecology,* 25**,** 391-403.
IMAMURA, T., ARIGA, H., KANEKO, M., WATANABE, M., SHIBUKAWA, Y., FUKUDA, Y., NAGASAWA, K., GOTO, A. & FUJIKI, T. 2013. Neurodevelopmental Outcomes of Children with Periventricular Leukomalacia. *Pediatrics & Neonatology,* 54**,** 367-372.
INGEMARSSON, I. 2003. Gender aspects of preterm birth. *BJOG: An International Journal of Obstetrics and Gynaecology,* 110**,** 34-38.
IVERSON, J. M. 2010. Developing language in a developing body: the relationship between motor development and language development. *Journal of Child Language,* 37**,** 229-261.
JACQUEMONT, S., COE, BRADLEY P., HERSCH, M., DUYZEND, MICHAEL H., KRUMM, N., BERGMANN, S., BECKMANN, JACQUES S., ROSENFELD, JILL A. & EICHLER, EVAN E. 2014. A Higher Mutational Burden in Females Supports a "Female Protective Model" in Neurodevelopmental Disorders. *American Journal of Human Genetics,* 94**,** 415-425.
JENG, S.-F., LAU, T.-W., HSIEH, W.-S., LUO, H.-J., CHEN, P.-S., LIN, K.-H. & SHIEH, J.-Y. 2008. Development of walking in preterm and term infants: Age of onset, qualitative features and sensitivity to resonance. *Gait & Posture,* 27**,** 340-346.
JIANG, S., LYU, Y., YE, X. Y., MONTERROSA, L., SHAH, P. S. & LEE, S. K. 2015. Intensity of delivery room resuscitation and neonatal outcomes in infants born at 33 to 36 weeks' gestation. *J Perinatol*.
JOBE, A. H. 2014. A risk of sensory deprivation in the neonatal intensive care unit. *J Pediatr,* 164**,** 1265-7.
JOHNSON, S. 2007. Cognitive and behavioural outcomes following very preterm birth. *Semin Fetal Neonatal Med,* 12**,** 363-73.
JOHNSON, S., EVANS, T. A., DRAPER, E. S., FIELD, D. J., MANKTELOW, B. N., MARLOW, N., MATTHEWS, R., PETROU, S., SEATON, S. E., SMITH, L. K. & BOYLE, E. M. 2015. Neurodevelopmental outcomes following late and moderate prematurity: a population-based cohort study. *Archives of Disease in Childhood. Fetal and Neonatal Edition,* 100**,** F301-F308.
JORQUERA-CABRERA, S., ROMERO-AYUSO, D., RODRIGUEZ-GIL, G. & TRIVIÑO-JUÁREZ, J.-M. 2017. Assessment of Sensory Processing Characteristics in Children between 3 and 11 Years Old: A Systematic Review. *Frontiers in Pediatrics,* 5**,** 57.
JOSE, M. A. & HARVEY, A. S. 2017. Thalamocortical Interactions for Sensory Processing. Interactive Factory.
JOVANOVIC, B. & SCHWARZER, G. 2011. Learning to grasp efficiently: the development of motor planning and the role of observational learning. *Vision Res,* 51**,** 945-54.
KANAGASABAI, P. S., MOHAN, D., LEWIS, L. E., KAMATH, A. & RAO, B. K. 2013. Effect of Multisensory Stimulation on Neuromotor Development in Preterm Infants. *The Indian Journal of Pediatrics,* 80**,** 460-464.
KANOLD, P. O. 2009. Subplate Neurons: Crucial Regulators of Cortical Development and Plasticity. *Frontiers in Neuroanatomy,* 3**,** 16.

KATZ, J., LEE, A. C. C., KOZUKI, N., LAWN, J. E., COUSENS, S., BLENCOWE, H., EZZATI, M., BHUTTA, Z. A., MARCHANT, T., WILLEY, B. A., ADAIR, L., BARROS, F., BAQUI, A. H., CHRISTIAN, P., FAWZI, W., GONZALEZ, R., HUMPHREY, J., HUYBREGTS, L., KOLSTEREN, P., MONGKOLCHATI, A., MULLANY, L. C., NDYOMUGYENYI, R., NIEN, J. K., OSRIN, D., ROBERFROID, D., SANIA, A., SCHMIEGELOW, C., SILVEIRA, M. F., TIELSCH, J., VAIDYA, A., VELAPHI, S. C., VICTORA, C. G., WATSON-JONES, D. & BLACK, R. E. 2013. Mortality risk in preterm and small-for-gestational-age infants in low-income and middle-income countries: a pooled country analysis. *The Lancet,* 382**,** 417-425.

KAYENNE, M. R. F. C. & LINHARES, M. B. 2011. Motor development curve from 0 to 12 months in infants born preterm. *Acta Paediatr,* 100**,** 379-84.

KELMANSON, I. A. & ADULAS, E. I. 2006. Massage therapy and sleep behaviour in infants born with low birth weight. *Complementary Therapies in Clinical Practice,* 12**,** 200-205.

KESAVAN, K. 2015. Neurodevelopmental Implications of Neonatal Pain and Morphine Exposure. *Pediatr Ann,* 44**,** e260-4.

KINNEY, H. C. 2006. The near-term (late preterm) human brain and risk for periventricular leukomalacia: a review. *Semin Perinatol,* 30**,** 81-8.

KNYAZEVA, M. G. 2013. Splenium of Corpus Callosum: Patterns of Interhemispheric Interaction in Children and Adults. *Neural Plasticity,* 2013**,** 12.

KOLB, B. & GIBB, R. 2014. Searching for the principles of brain plasticity and behavior. *Cortex,* 58**,** 251-260.

KOSTOVIC, I. & JOVANOV-MILOSEVIC, N. 2006. The development of cerebral connections during the first 20-45 weeks' gestation. *Semin Fetal Neonatal Med,* 11**,** 415-22.

KOTECHA, S. J., DUNSTAN, F. D. & KOTECHA, S. 2012. Long term respiratory outcomes of late preterm-born infants. *Seminars in Fetal and Neonatal Medicine,* 17**,** 77-81.

KOZIOL, L. F., BUDDING, D. E. & CHIDEKEL, D. 2012. From Movement to Thought: Executive Function, Embodied Cognition, and the Cerebellum. *The Cerebellum,* 11**,** 505-525.

KRAAN, C. M., TAN, A. H. J. & CORNISH, K. M. 2017. The developmental dynamics of gait maturation with a focus on spatiotemporal measures. *Gait & Posture,* 51**,** 208-217.

KUGELMAN, A. & COLIN, A. A. 2013. Late Preterm Infants: Near Term But Still in a Critical Developmental Time Period. *Pediatrics,* 132**,** 741.

KULKARNI, A., KAUSHIK, J. S., GUPTA, P., SHARMA, H. & AGRAWAL, R. K. 2010. Massage and touch therapy in neonates: The current evidence. *Indian Pediatrics,* 47**,** 771-776.

KUMAR, J., UPADHYAY, A., DWIVEDI, A. K., GOTHWAL, S., JAISWAL, V. & AGGARWAL, S. 2013. Effect of oil massage on growth in preterm neonates less than 1800 g: a randomized control trial. *Indian J Pediatr,* 80.

KYNØ, N. M., RAVN, I. H., LINDEMANN, R., FAGERLAND, M. W., SMEBY, N. A. & TORGERSEN, A. M. 2012. Effect of an early intervention programme on development of moderate and late preterm infants at 36 months: A randomized controlled study. *Infant Behavior and Development,* 35**,** 916-926.

LAI, M. M., D'ACUNTO, G., GUZZETTA, A., BOYD, R. N., ROSE, S. E., FRIPP, J., FINNIGAN, S., NGENDA, N., LOVE, P., WHITTINGHAM, K., PANNEK, K., WARE, R. S. & COLDITZ, P. B. 2016. PREMM: preterm early massage by the

mother: protocol of a randomised controlled trial of massage therapy in very preterm infants. *BMC Pediatrics,* 16**,** 1-12.
LAND, C. & SCHOENAU, E. 2008. Fetal and postnatal bone development: reviewing the role of mechanical stimuli and nutrition. *Best Practice and Research: Clinical Endocrinology and Metabolism,* 22**,** 107-118.
LAPTOOK, A. R. 2016. Birth Asphyxia and Hypoxic-Ischemic Brain Injury in the Preterm Infant. *Clinics in Perinatology,* 43**,** 529-545.
LATASH, M. L. 2010. Stages in Learning Motor Synergies: A View Based on the Equilibrium-Point Hypothesis. *Human movement science,* 29**,** 642-654.
LATASH, M. L., LEVIN, M. F., SCHOLZ, J. P. & SCHÖNER, G. 2010. Motor Control Theories and Their Applications. *Medicina (Kaunas, Lithuania),* 46**,** 382-392.
LAUGHON, M., O'SHEA, M. T., ALLRED, E. N., BOSE, C., KUBAN, K., VAN MARTER, L. J., EHRENKRANZ, R. A., LEVITON, A. & INVESTIGATORS, E. S. 2009. Chronic lung disease and developmental delay at 2 years of age in children born before 28 weeks' gestation. *Pediatrics,* 124**,** 637-648.
LAUGHTON, B., CORNELL, M., KIDD, M., SPRINGER, P. E., DOBBELS, E. F. M.-T., RENSBURG, A. J. V., OTWOMBE, K., BABIKER, A., GIBB, D. M., VIOLARI, A., KRUGER, M. & COTTON, M. F. 2018. Five year neurodevelopment outcomes of perinatally HIV-infected children on early limited or deferred continuous antiretroviral therapy. *Journal of the International AIDS Society,* 21**,** e25106.
LAW, J., SHAW, P., LEE, M. & SHELDON, M. 2014. From Saccades to Grasping: A Model of Coordinated Reaching Through Simulated Development on a Humanoid Robot. *IEEE Transactions on Autonomous Mental Development,* 6**,** 93-109.
LEE, H. 2005. The Effect of Infant Massage on Weight Gain, Physiological and Behavioral Responses in Premature Infants. *Journal of Korean Academy of Nursing,* 35**,** 1451 - 1460.
LEVINE, D., STROTHER-GARCIA, K., GOLINKOFF, R. & HIRSH-PASEK, K. 2016. Language Development in the First Year of Life: What Deaf Children Might Be Missing Before Cochlear Implantation. *Otology & Neurotology,* 37**,** e56 - e62.
LEVY, J., HABIB, R. H., LIPTSEN, E., SINGH, R., KAHN, D., STEELE, A. M. & COURTNEY, S. E. 2006. Prone versus supine positioning in the well preterm infant: Effects on work of breathing and breathing patterns. *Pediatric Pulmonology,* 41**,** 754-758.
LI, X., EIDEN, R. D., EPSTEIN, L. H., SHENASSA, E. D., XIE, C. & WEN, X. 2016. Etiological Subgroups of Small-for-Gestational-Age: Differential Neurodevelopmental Outcomes. *PLoS ONE,* 11**,** e0160677.
LICKLITER, R. 2011. The Integrated Development of Sensory Organization. *Clinics in perinatology,* 38**,** 591-603.
LINSELL, L., MALOUF, R., MORRIS, J., KURINCZUK, J. & MARLOW, N. 2015. Prognostic Factors for Poor Cognitive Development in Children Born Very Preterm or With Very Low Birth Weight: A Systematic Review. *JAMA Pediatrics,* 169**,** 1162 - 1172.
LITMANOVITZ, I., DOLFIN, T., ARNON, S., REGEV, R. H., NEMET, D. & ELIAKIM, A. 2007. Assisted exercise and bone strength in preterm infants. *Calcif Tissue Int,* 80**,** 39-43.
LOBO, M. A., HARBOURNE, R. T., DUSING, S. C. & MCCOY, S. W. 2013. Grounding Early Intervention: Physical Therapy Cannot Just Be About Motor Skills Anymore. *Physical Therapy,* 93**,** 94-103.

LOEPKE, A. W. 2010. Developmental neurotoxicity of sedatives and anesthetics: A concern for neonatal and pediatric critical care medicine?*. *Pediatric Critical Care Medicine,* 11**,** 217-226.

LUCAS-THOMPSON, R., TOWNSEND, E. L., GUNNAR, M. R., GEORGIEFF, M. K., GUIANG, S. F., CIFFUENTES, R. F., LUSSKY, R. C. & DAVIS, E. P. 2008. Developmental Changes in the Responses of Preterm Infants to a Painful Stressor. *Infant behavior & development,* 31**,** 614-623.

LUIZ, D. M., FOXCROFT, C. D. & POVEY, J.-L. 2006. The Griffiths scales of mental development : a factorial validity study. *South African Journal of Psychology,* 36**,** 192-214.

LUIZ, D. M., FOXCROFT, C. D. & STEWART, R. 2001. The construct validity of the Griffiths Scales of Mental Development. *Child: Care, Health and Development,* 27**,** 73-83.

LUTTIKHUIZEN DOS SANTOS, E. S., KIEVIET, J. F., KONIGS, M., ELBURG, R. M. & OOSTERLAAN, J. 2013. Predictive value of the Bayley scales of infant development on development of very preterm/very low birth weight children: a meta-analysis. *Early Hum Dev,* 89.

MA, L., YANG, B., MENG, L., WANG, B., ZHENG, C. & CAO, A. 2015. Effect of early intervention on premature infants' general movements. *Brain and Development,* 37**,** 387-393.

MACKIE, A. S., VATANPOUR, S., ALTON, G. Y., DINU, I. A., RYERSON, L., MODDEMANN, D. M., THOMAS PETRIE, J., ROBERTSON, C. M. T., JOFFE, A. R., ROSS, D. B., REBEYKA, I. M., SAUVE, R., BLAKLEY, P., SYNNES, A. & BODANI, J. 2015. Clinical Outcome Score Predicts Adverse Neurodevelopmental Outcome After Infant Heart Surgery. *The Annals of Thoracic Surgery,* 99**,** 2124-2132.

MADHAVAN, K. M., MCQUEENY, T., HOWE, S. R., SHEAR, P. & SZAFLARSKI, J. 2014. Superior Longitudinal Fasciculus and Language Functioning in Healthy Aging. *Brain research,* 1562**,** 11-22.

MADLINGER-LEWIS, L., REYNOLDS, L., ZAREM, C., CRAPNELL, T., INDER, T. & PINEDA, R. 2014. The Effects of Alternative Positioning on Preterm Infants in the Neonatal Intensive Care Unit: A Randomized Clinical Trial. *Research in developmental disabilities,* 35**,** 490-497.

MAGUIRE, C. M., WALTHER, F. J., VAN ZWIETEN, P. H. T., LE CESSIE, S., WIT, J. M. & VEEN, S. 2009a. Follow-up Outcomes at 1 and 2 Years of Infants Born Less Than 32 Weeks After Newborn Individualized Developmental Care and Assessment Program. *Pediatrics,* 123**,** 1081.

MAGUIRE, C. M., WALTHER, F. J., VAN ZWIETEN, P. H. T., LE CESSIE, S., WIT, J. M. & VEEN, S. 2009b. No change in developmental outcome with incubator covers and nesting for very preterm infants in a randomised controlled trial. *Archives of Disease in Childhood - Fetal and Neonatal Edition,* 94**,** F92.

MAHURIN SMITH, J., SEGEBART DETHORNE, L., LOGAN, J. A. R., CHANNELL, R. W. & PETRILL, S. A. 2014. Impact of Prematurity on Language Skills at School Age. *Journal of Speech, Language & Hearing Research,* 57**,** 901-916.

MAITRE, N. L., MARSHALL, D. D., PRICE, W. A., SLAUGHTER, J. C., O'SHEA, T. M., MAXFIELD, C. & GOLDSTEIN, R. F. 2009. Neurodevelopmental Outcome of Infants With Unilateral or Bilateral Periventricular Hemorrhagic Infarction. *Pediatrics,* 124**,** e1153-e1160.

MAJNEMER, A. & SNIDER, L. 2005. A comparison of developmental assessments of the newborn and young infant. *Mental Retardation & Developmental Disabilities Research Reviews,* 11**,** 68-73.

MALINA, R. M. 2004. Motor Development during Infancy and Early Childhood: Overview and Suggested Directions for Research. *International Journal of Sport and Health Science,* 2**,** 50-66.

MANANDHAR, S. R., DULAL, S., MANANDHAR, D. S., SAVILLE, N. & PROST, A. 2016. Acceptability and Reliability of the Bayley Scales of Infant Development III Cognitive and Motor Scales among Children in Makwanpur. *J Nepal Health Res Counc,* 14**,** 47-50.

MANUCK, T. A., RICE, M. M., BAILIT, J. L., GROBMAN, W. A., REDDY, U. M., WAPNER, R. J., THORP, J. M., CARITIS, S. N., PRASAD, M., TITA, A. T., SAADE, G. R., SOROKIN, Y., ROUSE, D. J., BLACKWELL, S. C., TOLOSA, J. E., EUNICE KENNEDY SHRIVER NATIONAL INSTITUTE OF CHILD, H. & HUMAN DEVELOPMENT MATERNAL-FETAL MEDICINE UNITS, N. 2016. Preterm Neonatal Morbidity and Mortality by Gestational Age: A Contemporary Cohort. *Am J Obstet Gynecol*.

MARCH OF DIMES, PMNCH, SAVE THE CHILDREN & WHO 2012. Born Too Soon: The Global action report on preterm Birth. *In:* HOWSON. CP, KINNEY. MV & LAWN. JV (eds.). Geneva: WHO.

MARTIN, C. R., DAMMANN, O., ALLRED, E. N., PATEL, S., O'SHEA, T. M., KUBAN, K. C. K. & LEVITON, A. 2010. Neurodevelopment of Extremely Preterm Infants who had Necrotizing Enterocolitis with or without Late Bacteremia. *The Journal of Pediatrics,* 157**,** 751-756.e1.

MASSARO, A. N., HAMMAD, T. A., JAZZO, B. & ALY, H. 2009. Massage with kinesthetic stimulation improves weight gain in preterm infants. *J Perinatol,* 29.

MCANULTY, G. B., BUTLER, S. C., BERNSTEIN, J. H., ALS, H., DUFFY, F. H. & ZURAKOWSKI, D. 2009. Effects of the Newborn Individualized Developmental Care and Assessment Program (NIDCAP) at Age 8 Years: Preliminary Data. *Clinical Pediatrics,* 49**,** 258-270.

MCCREA, H. J. & MENT, L. R. 2008. The Diagnosis, Management, and Postnatal Prevention of Intraventricular Hemorrhage in the Preterm Neonate. *Clinics in Perinatology,* 35**,** 777-792.

MCGOWAN, J. E., ALDERDICE, F. A., DORAN, J., HOLMES, V. A., JENKINS, J., CRAIG, S. & JOHNSTON, L. 2012. Impact of neonatal intensive care on late preterm infants: developmental outcomes at 3 years. *Pediatrics,* 130**,** e1105-12.

MCGOWAN, J. E., ALDERDICE, F. A., HOLMES, V. A. & JOHNSTON, L. 2011. Early Childhood Development of Late-Preterm Infants: A Systematic Review. *Pediatrics*.

MCMAHON, E., WINTERMARK, P. & LAHAV, A. 2012. Auditory brain development in premature infants: the importance of early experience. *Annals of the New York Academy of Sciences,* 1252**,** 17-24.

MCMANUS, B. M., CARLE, A. C. & POEHLMANN, J. 2012. Effectiveness of Part C Early Intervention Physical, Occupational, and Speech Therapy Services for Preterm or Low Birth Weight Infants in Wisconsin, United States. *Academic pediatrics,* 12**,** 96-103.

MCMILLAN, S. S., KING, M. & TULLY, M. P. 2016. How to use the nominal group and Delphi techniques. *International Journal of Clinical Pharmacy,* 38**,** 655-662.

MEISTER, I. G., BOROOJERDI, B., FOLTYS, H., SPARING, R., HUBER, W. & TÖPPER, R. 2003. Motor cortex hand area and speech: implications for the development of language. *Neuropsychologia,* 41**,** 401-406.

MERCIER, C. E., DUNN, M. S., FERRELLI, K. R., HOWARD, D. B., SOLL, R. F. & AND THE VERMONT OXFORD NETWORK, E. I. F.-U. S. G. 2010.

Neurodevelopmental Outcome of Extremely Low Birth Weight Infants from the Vermont Oxford Network: 1998–2003. *Neonatology,* 97**,** 329-338.
MERHAR, S. L., TABANGIN, M. E., MEINZEN-DERR, J. & SCHIBLER, K. R. 2012. Grade and Laterality of Intraventricular Hemorrhage to Predict 18–22 Month Neurodevelopmental Outcomes in Extremely Low Birth Weight Infants. *Acta paediatrica (Oslo, Norway : 1992),* 101**,** 414-418.
MESA, E. G. & PERAL, J. A. H. 2011. Incidence and Costs of Multifetal Pregnancies in Andalusia (2000–2010). *Twin Research and Human Genetics,* 14**,** 484-489.
MICHALOWICZ, B. & DURAND, R. 2007. Maternal periodontal disease and spontaneous preterm birth. *Periodontology 2000,* 44**,** 103 - 112.
MILGROM, J., NEWNHAM, C., ANDERSON, P. J., DOYLE, L. W., GEMMILL, A. W., LEE, K., HUNT, R. W., BEAR, M. & INDER, T. 2010. Early Sensitivity Training for Parents of Preterm Infants: Impact on the Developing Brain. *Pediatr Res,* 67**,** 330-335.
MILGROM, J., NEWNHAM, C., MARTIN, P. R., ANDERSON, P. J., DOYLE, L. W., HUNT, R. W., ACHENBACH, T. M., FERRETTI, C., HOLT, C. J., INDER, T. E. & GEMMILL, A. W. 2013. Early communication in preterm infants following intervention in the NICU. *Early Human Development,* 89**,** 755-762.
MILNE, S., MCDONALD, J. & COMINO, E. J. 2012. The Use of the Bayley Scales of Infant and Toddler Development III with Clinical Populations: A Preliminary Exploration. *Physical & Occupational Therapy In Pediatrics,* 32**,** 24-33.
MILNE S, M. J., COMINO J 2012. The Use of the Bayley Scales of Infant and Toddler Development III with Clinical Populations: A Preliminary Exploration. *Physical & Occupational Therapy in Pediatrics,* 32**,** 24-33.
MITCHELL, A. W., MOORE, E. M., ROBERTS, E. J., HACHTEL, K. W. & BROWN, M. S. 2015. Sensory Processing Disorder in Children Ages Birth-3 Years Born Prematurely: A Systematic Review. *American Journal of Occupational Therapy January/February,* 69**,** 69012200301-690122003011.
MONANGI, N. K., BROCKWAY, H. M., HOUSE, M., ZHANG, G. & MUGLIA, L. J. 2015. The genetics of preterm birth: Progress and promise. *Semin Perinatol*.
MONTIROSSO, R., GIUSTI, L., DEL PRETE, A., ZANINI, R., BELLU, R., BORGATTI, R. & GROUP, N.-A. S. 2016. Language outcomes at 36 months in prematurely born children is associated with the quality of developmental care in NICUs. *J Perinatol,* 36**,** 768-774.
MOODY, C., CALLAHAN, T. J., ALDRICH, H., GANCE-CLEVELAND, B. & SABLES-BAUS, S. 2017. Early Initiation of Newborn Individualized Developmental Care and Assessment Program (NIDCAP) Reduces Length of Stay: A Quality Improvement Project. *Journal of Pediatric Nursing,* 32**,** 59-63.
MOON, C., LAGERCRANTZ, H. & KUHL, P. K. 2013. Language experienced in utero affects vowel perception after birth: a two-country study. *Acta paediatrica (Oslo, Norway : 1992),* 102**,** 156-160.
MOORE, T., HENNESSY, E. M., MYLES, J., JOHNSON, S. J., DRAPER, E. S., COSTELOE, K. L. & MARLOW, N. 2012a. Neurological and developmental outcome in extremely preterm children born in England in 1995 and 2006: the EPICure studies. *BMJ : British Medical Journal,* 345.
MOORE, T., JOHNSON, S., HAIDER, S., HENNESSY, E. & MARLOW, N. 2012b. Relationship between test scores using the second and third editions of the Bayley Scales in extremely preterm children. *J Pediatr,* 160**,** 553-8.
MORAG, I., ROTEM, I., FRISCH, M., HENDLER, I., SIMCHEN, M. J., LEIBOVITZ, L., MAAYAN-METZGER, A. & STRAUSS, T. 2017. Cumulative pain-related stress

and developmental outcomes among low-risk preterm infants at one year corrected age. *Early Human Development,* 109**,** 1-5.
MORLEY, C. J., DAVIS, P. G., DOYLE, L. W., BRION, L. P., HASCOET, J.-M. & CARLIN, J. B. 2008. Nasal CPAP or Intubation at Birth for Very Preterm Infants. *New England Journal of Medicine,* 358**,** 700-708.
MOSTER, D., TERJE LIE, R. & MARKESTAD, T. 2008. Longterm medical and social consequences of preterm birth. *The New England Journal of Medicine,* 359**,** 262 - 273.
MOYER-MILEUR, L., LUETKEMEIER, M., BOOMER, L. & CHAN, G. 1995. Effect of physical activity on bone mineralization in premature infants. *The Journal of Pediatrics,* 127**,** 620 - 625.
MOYER-MILEUR, L. J., BALL, S. D., BRUNSTETTER, V. L. & CHAN, G. M. 2008. Maternal-administered physical activity enhances bone mineral acquisition in premature very low birth weight infants. *J Perinatol,* 28**,** 432-437.
MOYER-MILEUR, L. J., HALEY, S., SLATER, H., BEACHY, J. & SMITH, S. L. 2013. Massage improves growth quality by decreasing body fat deposition in male preterm infants. *The Journal of pediatrics,* 162**,** 490-495.
MUGLIA, L. J. & KATZ, M. 2010. The Enigma of Spontaneous Preterm Birth. *New England Journal of Medicine,* 362**,** 529-535.
MÜRNER-LAVANCHY, I., STEINLIN, M., KIEFER, C., WEISSTANNER, C., RITTER, B. C., PERRIG, W. & EVERTS, R. 2014. Delayed Development of Neural Language Organization in Very Preterm Born Children. *Developmental Neuropsychology,* 39**,** 529-542.
MURPHY, K. E., WILLAN, A. R., HANNAH, M. E., OHLSSON, A., KELLY, E. N., MATTHEWS, S. G., SAIGAL, S., ASZTALOS, E., ROSS, S., DELISLE, M.-F., AMANKWAH, K., GUSELLE, P., GAFNI, A., LEE, S. K. & ARMSON, B. A. 2012. Effect of Antenatal Corticosteroids on Fetal Growth and Gestational Age at Birth. *Obstetrics & Gynecology,* 119**,** 917-923.
MURRAY, S. R., STOCK, S. J. & NORMAN, J. E. 2017. Long-term childhood outcomes after interventions for prevention and management of preterm birth. *Seminars in Perinatology,* 41**,** 519-527.
NAUMBURG, E., STROMBERG, B. & KIELER, H. 2012. Prenatal Characteristics of Infants with a Neuronal Migration Disorder: A National-Based Study. *International Journal of Pediatrics,* 2012**,** 5.
NAVARRETE, C. T., WRAGE, L. A., CARLO, W. A., WALSH, M. C., RICH, W., GANTZ, M. G., DAS, A., SCHIBLER, K., NEWMAN, N. S., PIAZZA, A. J., POINDEXTER, B. B., SHANKARAN, S., SÁNCHEZ, P. J., MORRIS, B. H., FRANTZ III, I. D., VAN MEURS, K. P., COTTEN, C. M., EHRENKRANZ, R. A., BELL, E. F., WATTERBERG, K. L., HIGGINS, R. D., DUARA, S., DAS, A., GANTZ, M., JOBE, A. H., CAPLAN, M. S., FANAROFF, A. A., WILSON-COSTELLO, D. E., SINER, B. S., ZADELL, A., DIFIORE, J., BHOLA, M., FRIEDMAN, H. G., YALCINKAYA, G., DONOVAN, E. F., NARENDRAN, V., YOLTON, K., BRIDGES, K., ALEXANDER, B., GRISBY, C., MERSMANN, M. W., MINCEY, H. L., HESSLING, J., GRATTON, T. L., GOLDBERG, R. N., GOLDSTEIN, R. F., ASHLEY, P., AUTEN, K. J., FISHER, K. A., FOY, K. A., FREEDMAN, S. F., GUSTAFSON, K. E., LOHMEYER, M. B., MALCOLM, W. F., WALLACE, D. K., STOLL, B. J., ADAMS-CHAPMAN, I., BUCHTER, S., CARLTON, D. P., CARTER, S., FRITZ, S., HALE, E. C., HUTCHINSON, A. K., LAROSSA, M. M., SMIKLE, G. V., ARCHER, S. W., DUSICK, A. M., LEMONS, J. A., MYERS, G. J., WILSON, L. D., HAMER, F., COOK, A. B., HERRON, D. E.,

LYTLE, C., MINNICH, H. M., BERBERICH, M. A., BLAISDELL, C. J., GAIL, D. B., KILEY, J. P., POOLE, W. K., NEWMAN, J. E., HASTINGS, B. K., O'DONNELL AUMAN, J., HUITEMA, C. P., PICKETT II, J. W., WALLACE, D., ZATERKA-BAXTER, K. M., STEVENSON, D. K., HINTZ, S. R., BALL, M. B., BENTLEY, B., BRUNO, E. F., DAVIS, A. S., DEANDA, M. E., DEBATTISTA, A. M., HUFFMAN, L. C., KOHN, J. G., PROUD, M. S., PYLE, R. P., ST. JOHN, N. H., et al. 2016. Growth Outcomes of Preterm Infants Exposed to Different Oxygen Saturation Target Ranges from Birth. *The Journal of Pediatrics*.

NEMEC STEFAN, F., NEMEC, U., BRUGGER PETER, C., BETTELHEIM, D., ROTMENSCH, S., GRAHAM JOHN, M., RIMOIN DAVID, L. & PRAYER, D. 2012. MR imaging of the fetal musculoskeletal system. *Prenatal Diagnosis,* 32**,** 205-213.

NEMET, D., DOLFIN, T., LITMANOWITZ, I., SHAINKIN-KESTENBAUM, R., LIS, M. & ELIAKIM, A. 2002. Evidence for Exercise-Induced Bone Formation in Premature Infants. *International Journal of Sports Medicine,* 23**,** 82 - 85.

NEWNHAM, C. A., MILGROM, J. & SKOUTERIS, H. 2009. Effectiveness of a Modified Mother–Infant Transaction Program on Outcomes for Preterm Infants from 3 to 24 months of age. *Infant Behavior and Development,* 32**,** 17-26.

NGOC, N. T. N., MERIALDI, M., ABDEL-ALEEM, H., CARROLI, G., PURWAR, M., ZAVALETA, N., CAMPÓDONICO, L., ALI, M. M., HOFMEYR, G. J. & MATHAI, M. 2006. Causes of stillbirths and early neonatal deaths: data from 7993 pregnancies in six developing countries. *Bulletin of the World Health Organization,* 84**,** 699-705.

NIGHTLINGER, K. 2011. Developmentally Supportive Care in the Neonatal Intensive Care Unit: An Occupational Therapist's Role. *Neonatal Network,* 30**,** 243-248.

NORDHOV, S. M., RONNING, J. A., DAHL, L. B., ULVUND, S. E., TUNBY, J. & KAARESEN, P. I. 2010. Early intervention improves cognitive outcomes for preterm infants: randomized controlled trial. *Pediatrics,* 126**,** e1088-94.

O'CONNOR, D. L., JACOBS, J., HALL, R., ADAMKIN, D., AUESTAD, N., CASTILLO, M., CONNOR, W. E., CONNOR, S. L., FITZGERALD, K., GROH-WARGO, S., HARTMANN, E. E., JANOWSKY, J., LUCAS, A., MARGESON, D., MENA, P., NEURINGER, M., ROSS, G., SINGER, L., STEPHENSON, T., SZABO, J. & ZEMON, V. 2003. Growth and Development of Premature Infants Fed Predominantly Human Milk, Predominantly Premature Infant Formula, or a Combination of Human Milk and Premature Formula. *Journal of Pediatric Gastroenterology and Nutrition,* 37**,** 437-446.

O'REILLY, R., GRINDLE, C., ZWICKY, E. F. & MORLET, T. 2011. Development of the Vestibular System and Balance Function: Differential Diagnosis in the Pediatric Population. *Otolaryngologic Clinics of North America,* 44**,** 251-271.

OBERG, G., CAMPBELL, S., GIROLAMI, G., USTAD, T., JORGENSEN, L. & KAARESEN, P. 2012. Study Protocol: an early intervention program to improve motor outcome in preterm infants: a randomized controlled trial and qualitative study of physiotherapy performance and parental experiences. *BMC Pediatrics,* 12**,** doi: 10.1186/1471-2431-12-15.

ODD, D. E., EMOND, A. & WHITELAW, A. 2012. Long-term cognitive outcomes of infants born moderately and late preterm. *Developmental Medicine & Child Neurology,* 54**,** 704-709.

OHLSSON, A. & JACOBS, S. E. 2013. NIDCAP: a systematic review and meta-analyses of randomized controlled trials. *Pediatrics,* 131**,** e881-93.

ORTIZ-MANTILLA, S., CHOUDHURY, N., LEEVERS, H. & BENASICH, A. A. 2008. Understanding language and cognitive deficits in very low birth weight children. *Dev Psychobiol,* 50**,** 107-26.

PADILLA, N., FALCÓN, C., SANZ-CORTÉS, M., FIGUERAS, F., BARGALLO, N., CRISPI, F., EIXARCH, E., ARRANZ, A., BOTET, F. & GRATACÓS, E. 2011. Differential effects of intrauterine growth restriction on brain structure and development in preterm infants: A magnetic resonance imaging study. *Brain Research,* 1382**,** 98-108.

PAQUETTE, N., VANNASING, P., TREMBLAY, J., LEFEBVRE, F., ROY, M.-S., MCKERRAL, M., LEPORE, F., LASSONDE, M. & GALLAGHER, A. 2015. Early electrophysiological markers of atypical language processing in prematurely born infants. *Neuropsychologia,* 79, Part A**,** 21-32.

PATEL, D. S. & GREENOUGH, A. 2008. Does nasal CPAP reduce bronchopulmonary dysplasia (BPD)? *Acta Paediatrica,* 97**,** 1314-1317.

PATERSON, S. J., HEIM, S., FRIEDMAN, J. T., CHOUDHURY, N. & BENASICH, A. A. 2006. Development of structure and function in the infant brain: Implications for cognition, language and social behaviour. *Neuroscience and biobehavioral reviews,* 30**,** 1087-1105.

PEACOCK, J. L., MARSTON, L., MARLOW, N., CALVERT, S. A. & GREENOUGH, A. 2012. Neonatal and infant outcome in boys and girls born very prematurely. *Pediatric Research,* 71**,** 305.

PELTONIEMI, O. M., KARI, M. A. & HALLMAN, M. 2011. Repeated antenatal corticosteroid treatment: a systematic review and meta-analysis. *Acta Obstetricia et Gynecologica Scandinavica,* 90**,** 719-727.

PENG, W., ZHU, H., SHI, H. & LIU, E. 2014. Volume-targeted ventilation is more suitable than pressure-limited ventilation for preterm infants: a systematic review and meta-analysis. *Archives of Disease in Childhood - Fetal and Neonatal Edition,* 99**,** F158.

PERSSON, J., NYBERG, L., LIND, J., LARSSON, A., NILSSON, L.-G., INGVAR, M. & BUCKNER, R. L. 2005. Structure–function correlates of cognitive decline in aging. *Cerebral cortex,* 16**,** 907-915.

PETERS, K. L., ROSYCHUK, R. J., HENDSON, L., COTE, J. J., MCPHERSON, C. & TYEBKHAN, J. M. 2009. Improvement of short- and long-term outcomes for very low birth weight infants: Edmonton NIDCAP trial. *Pediatrics,* 124**,** 1009-20.

PEYTON, C., YANG, E., MSALL, M. E., ADDE, L., STØEN, R., FJØRTOFT, T., BOS, A. F., EINSPIELER, C., ZHOU, Y., SCHREIBER, M. D., MARKS, J. D. & DROBYSHEVSKY, A. 2016. White Matter Injury and General Movements in High-Risk Preterm Infants. *American Journal of Neuroradiology*.

PHILPOTT-ROBINSON, K., LANE, S. J., KOROSTENSKI, L. & LANE, A. E. 2017. The impact of the Neonatal Intensive Care Unit on sensory and developmental outcomes in infants born preterm: A scoping review. *British Journal of Occupational Therapy,* 80**,** 459-469.

PICCIOLINI, O., SQUARZA, C., FONTANA, C., GIANNI, M. L., CORTINOVIS, I., GANGI, S., GARDON, L., PRESEZZI, G., FUMAGALLI, M. & MOSCA, F. 2015. Neurodevelopmental outcome of extremely low birth weight infants at 24 months corrected age: a comparison between Griffiths and Bayley Scales. *BMC Pediatr,* 15**,** 139.

PICHEANSATHIAN, W. & PATCHAREE, W. 2005. A Systematic Review of Positioning of Preterm Infants for Optimal Physiological Development. *JBI Database of Systematic Reviews and Implementation Reports,* 3**,** 1-11.

PICHEANSATHIAN, W., WORAGIDPOONPOL, P. & BAOSOUNG, C. 2009. Positioning of Preterm Infants for Optimal Physiological Development: a systematic review. *JBI Database of Systematic Reviews and Implementation Reports,* 7**,** 224-259.
PIEK, J. P., DAWSON, L., SMITH, L. M. & GASSON, N. 2008. The role of early fine and gross motor development on later motor and cognitive abilities. *Hum Mov Sci,* 27.
PINEDA, R., GUTH, R., HERRING, A., REYNOLDS, L., OBERLE, S. & SMITH, J. 2016. Enhancing sensory experiences for very preterm infants in the NICU: an integrative review. *Journal Of Perinatology,* 37**,** 323.
POLYAK, A., ROSENFELD, J. A. & GIRIRAJAN, S. 2015. An assessment of sex bias in neurodevelopmental disorders. *Genome Medicine,* 7**,** 94.
POORE, M. A. & BARLOW, S. M. 2009. Suck Predicts Neuromotor Integrity and Developmental Outcomes. *Perspectives on Speech Science and Orofacial Disorders,* 19**,** 44 - 51.
POTTER M, G. S. A. H. P. 2004. The Nominal Group Technique: A useful consesnus methodology in physiotherapy reserach. *New Zealand Journal of Physiotherapy,* 32**,** 126-130.
POTTERTON, J., STEWART, A., COOPER, P. & BECKER, P. 2010. The effect of a basic home stimulation programme on the development of young children infected with HIV. *Developmental Medicine & Child Neurology,* 52**,** 547-551.
POULSEN, G., WOLKE, D., KURINCZUK, J. J., BOYLE, E. M., FIELD, D., ALFIREVIC, Z. & QUIGLEY, M. A. 2013. Gestational age and cognitive ability in early childhood: a population-based cohort study. *Paediatr Perinat Epidemiol,* 27**,** 371-9.
POWELL, T. W. 2008. The Use of Nonspeech Oral Motor Treatments for Developmental Speech Sound Production Disorders: Interventions and Interactions. *Language, Speech, and Hearing services in schools,* 39**,** 374 - 379.
PROCIANOY, R. S., MENDES, E. W. & SILVEIRA, R. C. 2010. Massage therapy improves neurodevelopment outcome at two years corrected age for very low birth weight infants. *Early Hum Dev,* 86.
PURISCH, S. E. & GYAMFI-BANNERMAN, C. 2017. Epidemiology of preterm birth. *Seminars in Perinatology,* 41**,** 387-391.
RAATIKAINEN, K., HEISKANEN, N. & HEINONEN, S. 2007. Under-attending free antenatal care is associated with adverse pregnancy outcomes. *BMC Public Health,* 7**,** 268.
RADEMEYER, V. & JACKLIN, L. 2013. A study to evaluate the performance of black South African urban infants on the Bayley Scales of Infant Development III. *South African Journal of Child Health,* 7**,** 54.
RAMACHANDRAN, S. & DUTTA, S. 2013. Early developmental care interventions of preterm very low birth weight infants. *Indian Pediatrics,* 50**,** 765-770.
RAMENGHI, L. A., RICCI, D., MERCURI, E., GROPPO, M., DE CARLI, A., OMETTO, A., FUMAGALLI, M., BASSI, L., PISONI, S., CIONI, G. & MOSCA, F. 2010. Visual performance and brain structures in the developing brain of pre-term infants. *Early Human Development,* 86**,** 73-75.
RAUCH, F. & SCHOENAU, E. 2002. Skeletal development in premature infants: a review of bone physiology beyond nutritional aspects. *Archives of Disease in Childhood - Fetal and Neonatal Edition,* 86**,** F82.
REES, C. M., PIERRO, A. & EATON, S. 2007. Neurodevelopmental outcomes of neonates with medically and surgically treated necrotizing enterocolitis. *Archives of Disease in Childhood - Fetal and Neonatal Edition,* 92**,** F193.
RESCH, B., NEUBAUER, K., HOFER, N., RESCH, E., MAURER, U., HAAS, J. & MÜLLER, W. 2012. Episodes of hypocarbia and early-onset sepsis are risk factors for

cystic periventricular leukomalacia in the preterm infant. *Early Human Development,* 88**,** 27-31.
RICHARDS, J. L., DREWS-BOTSCH, C., SALES, J. M., FLANDERS, W. D. & KRAMER, M. R. 2016. Describing the Shape of the Relationship Between Gestational Age at Birth and Cognitive Development in a Nationally Representative U.S. Birth Cohort. *Paediatric and Perinatal Epidemiology,* 30**,** 571-582.
RICHTER, L., HSIAO, C. & MABASO, M. 2016. Predictive power of psychometric assessments to identify young learners in need of early intervention : data from the Birth to Twenty Plus Cohort, South Africa. *South African Journal of Psychology,* 46**,** 175-190.
RICHTER, L. M. & GRIESEL, R. D. 1988. *Bayley scales of infant development : norms for interpreting the performance of Black South African infants,* Pretoria, Institute for Behavioural Sciences, University of South Africa.
ROAN, C. & BELL, A. 2017. Occupational Therapy in the Neonatal Intensive Care Unit for a Neonate with Perinatal Stroke: A Case Report. *Physical & Occupational Therapy In Pediatrics,* 37**,** 283-291.
ROBBINS, T. W. 2011. Cognition: The Ultimate Brain Function. *Neuropsychopharmacology,* 36**,** 1-2.
ROBERTS, D., BROWN, J., MEDLEY, N. & DALZIEL, S. R. 2017. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. *Cochrane Database of Systematic Reviews*.
ROBERTS, J. C., JAVED, M. J., HOCKER, J. R., WANG, H. & TARANTINO, M. D. 2018. Risk factors associated with intraventricular hemorrhage in extremely premature neonates. *Blood Coagulation & Fibrinolysis,* 29**,** 25-29.
ROBERTS, R. E., ANDERSON, E. J. & HUSAIN, M. 2013. White Matter Microstructure and Cognitive Function. *The Neuroscientist,* 19**,** 8-15.
ROBINSON, E. B., LICHTENSTEIN, P., ANCKARSÄTER, H., HAPPÉ, F. & RONALD, A. 2013. Examining and interpreting the female protective effect against autistic behavior. *Proceedings of the National Academy of Sciences,* 110**,** 5258.
ROLAND, P. E., HILGETAG, C. C. & DECO, G. 2014. Cortico-cortical communication dynamics. *Frontiers in Systems Neuroscience,* 8**,** 19.
ROLLER, M., LAZARO, R., BYL, N. & UMPHRED, D. 2012. Contemporary Issues and Theories of Motor Control, Motor Learning, and Neuroplasticity. *Neurological Rehabilitation 6th Edition.* Mosby.
ROPARS, S., TESSIER, R., CHARPAK, N. & URIZA, L. F. 2018. The long-term effects of the Kangaroo Mother Care intervention on cognitive functioning: Results from a longitudinal study. *Developmental Neuropsychology,* 43**,** 82-91.
ROSE, J., VASSAR, R., CAHILL-ROWLEY, K., STECHER GUZMAN, X., HINTZ, S. R., STEVENSON, D. K. & BARNEA-GORALY, N. 2014. Neonatal physiological correlates of near-term brain development on MRI and DTI in very-low-birth-weight preterm infants. *NeuroImage : Clinical,* 5**,** 169-177.
ROSENBLUM, A. & JOSMAN, N. 2003. The Relationship Between Postural Control and Fine Manual Dexterity. *Physical & Occupational Therapy in Pediatrics,* 23**,** 47-60.
ROTHBART, M. K., SHEESE, B. E., RUEDA, M. R. & POSNER, M. I. 2011. Developing Mechanisms of Self-Regulation in Early Life. *Emotion Review,* 3**,** 207-213.
ROVEE-COLLIER, C. & CUEVAS, K. 2009. Multiple memory systems are unnecessary to account for infant memory development: An ecological model. *Developmental Psychology,* 45**,** 160-174.

ROZE, E., KERSTJENS, J. M., MAATHUIS, C. G., TER HORST, H. J. & BOS, A. F. 2008. Risk factors for adverse outcome in preterm infants with periventricular hemorrhagic infarction. *Pediatrics,* 122**,** e46-52.
SAEADI, R., GHORBANI, Z. & SHAPOURI, M. A. 2015. The effect of massage with medium-chain triglyceride oil on weight gain in premature neonates. *Acta Medica Iran,* 53.
SALANDY, S., RAI, R., GUTIERREZ, S., ISHAK, B. & TUBBS, R. S. 2019. Neurological examination of the infant. *Clinical Anatomy,* 0.
SALMASO, N., JABLONSKA, B., SCAFIDI, J., VACCARINO, F. M. & GALLO, V. 2014. Neurobiology of premature brain injury. *Nature Neuroscience,* 17**,** 341-346.
SAMUELS, A., SLEMMING, W. & BALTON, S. 2012. Early Childhood Intervention in South Africa in Relation to the Developmental Systems Model. *Infants & Young Children,* 25**,** 334-345.
SANTOS, D. C. C., GABBARD, C. & GONCALVES, V. M. G. 2001. Motor Development During the First Year: A Comparative Study. *Journal of Genetic Psychology,* 162**,** 143.
SANTOS, J., PEARCE, S. E. & STROUSTRUP, A. 2015. Impact of Hospital-Based Environmental Exposures on Neurodevelopmental Outcomes of Preterm Infants. *Current opinion in pediatrics,* 27**,** 254-260.
SARAPUK, I. M., PAVLYSHYN, H. A., LACINA, L. & KRÓLAK-OLEJNIK, B. 2017. NEURODEVELOPMENTAL CARE OF PRETERM BABIES AND ITS KEY ELEMENTS. *International Journal of Medicine and Medical Research; No 1 (2017).*
SATHISH, Y., EDWARD LEWIS, L., ANGELITTA NORONHA, J., GEORGE, A., SNAYAK, B., S PAI, M., BHAT, R. & PURKAYASTHA, J. 2017. Clinical Outcomes of Snuggle up Position Using Positioning Aids for Preterm (27-32 Weeks) Infants. *Iranian Journal of Neonatology IJN,* 8**,** 1-6.
SAUNAVAARA, V., KALLANKARI, H., PARKKOLA, R., HAATAJA, L., OLSÉN, P., HALLMAN, M. & KAUKOLA, T. 2017. Very preterm children with fetal growth restriction demonstrated altered white matter maturation at nine years of age. *Acta Paediatrica,* 106**,** 1600-1607.
SCHANLER, R. J. 2011. Outcomes of Human Milk-Fed Premature Infants. *Seminars in Perinatology,* 35**,** 29-33.
SCHIRMER, C. R., PORTUGUES, M. W. & NUNES, M. L. 2006. Clinical assessment of language development in children at age 3 years that were born preterm. *Arquivos de Neuro-Psiquiatria,* 64**,** 926 - 931.
SCHLAPBACH, L. J., AEBISCHER, M., ADAMS, M., NATALUCCI, G., BONHOEFFER, J., LATZIN, P., NELLE, M., BUCHER, H. U., LATAL, B. & SWISS NEONATAL, N. 2011. Impact of sepsis on neurodevelopmental outcome in a Swiss National Cohort of extremely premature infants. *Pediatrics,* 128.
SCHMIDT, R. 1975. A schema theory of discrete motor skill learning. *Psychological Review,* 82**,** 225-260.
SCHONHAUT, L., ARMIJO, I. & PEREZ, M. 2015. Gestational age and developmental risk in moderately and late preterm and early term infants. *Pediatrics,* 135**,** e835-41.
SHAH, D. K., DOYLE, L. W., ANDERSON, P. J., BEAR, M., DALEY, A. J., HUNT, R. W. & INDER, T. E. 2008. Adverse Neurodevelopment in Preterm Infants with Postnatal Sepsis or Necrotizing Enterocolitis is Mediated by White Matter Abnormalities on Magnetic Resonance Imaging at Term. *The Journal of Pediatrics,* 153**,** 170-175.e1.
SHAKER, C. S. 2013. Cue-based feeding in the NICU: using the infant's communication as a guide. *Neonatal Network,* 32**,** 404.

SHAPIRO-MENDOZA, C., KOTELCHUCK, M., BARFIELD, W., DAVIN, C. A., DIOP, H., SILVER, M. & MANNING, S. E. 2013. Enrollment in early intervention programs among infants born late preterm, early term, and term. *Pediatrics,* 132**,** e61-9.

SHAW, S., SANKAR, M., THUKRAL, A., NATARAJAN, C., DEORARI, A., PAUL, V. & AGARWAL, R. 2018. Assisted Physical Exercise for Improving Bone Strength in Preterm Infants Less than 35 Weeks Gestation: A Randomized Controlled Trial. *Indian Pediatrics,* 55**,** 115-120.

SHEA, C. A., ROLFE, R. A. & MURPHY, P. 2015. The importance of foetal movement for co-ordinated cartilage and bone development in utero : clinical consequences and potential for therapy. *Bone & Joint Research,* 4**,** 105-116.

SHEEHAN, D. P. & KATZ, L. 2013. The effects of a daily, 6-week exergaming curriculum on balance in fourth grade children. *Journal of Sport and Health Science,* 2**,** 131-137.

SHERRINGTON, C. 1920. *The Interactive Action of the Nervous System,* New Haven Yale University Press.

SHIELDS, N. 2016. Three weeks of parent-administered physiotherapy for very preterm infants improves motor performance at 37 weeks more than usual care [synopsis]. *Journal of Physiotherapy*.

SHIOZAKI, A., MATSUDA, Y., SATOH, S. & SAITO, S. 2011. Impact of fetal sex in pregnancy-induced hypertension and preeclampsia in Japan. *Journal of Reproductive Immunology,* 89**,** 133-139.

SHULHAN, J., DICKEN, B., HARTLING, L. & LARSEN, B. M. 2017. Current Knowledge of Necrotizing Enterocolitis in Preterm Infants and the Impact of Different Types of Enteral Nutrition Products. *Adv Nutr,* 8**,** 80-91.

SIMMONS, L. E., RUBENS, C. E., DARMSTADT, G. L. & GRAVETT, M. G. 2010. Preventing Preterm Birth and Neonatal Mortality: Exploring the Epidemiology, Causes, and Interventions. *Seminars in Perinatology,* 34**,** 408-415.

SIMMS, V., CRAGG, L., GILMORE, C., MARLOW, N. & JOHNSON, S. 2013. Mathematics difficulties in children born very preterm: current research and future directions. *Archives of Disease in Childhood - Fetal and Neonatal Edition,* 98**,** F457.

SIVERT, W. L. 2011. *Joint compression therapy in the prevention of osteopenia of prematurity: Current research and future considerations.* Master of Arts in Nursing, Neonatal Nurse Practitioner Option, St. Catherine University.

SLYKERMAN, R. F., THOMPSON, J. M. D., CLARK, P. M., BECROFT, D. M. O., ROBINSON, E., PRYOR, J. E., WILD, C. J. & MITCHELL, E. A. 2007. Determinants of developmental delay in infants aged 12 months. *Paediatric and Perinatal Epidemiology,* 21**,** 121-128.

SMITH, G. C., GUTOVICH, J., SMYSER, C., PINEDA, R., NEWNHAM, C., TJOENG, T. H., VAVASSEUR, C., WALLENDORF, M., NEIL, J. & INDER, T. 2011. Neonatal intensive care unit stress is associated with brain development in preterm infants. *Annals of Neurology,* 70**,** 541-549.

SMITH, J. R. 2012. Comforting touch in the very preterm hospitalized infant: an integrative review. *Adv Neonatal Care,* 12.

SOHR-PRESTON, S. L. & SCARAMELLA, L. V. 2006. Implications of timing of maternal depressive symptoms for early cognitive and language development. *Clinical Child And Family Psychology Review,* 9**,** 65-83.

SOLTIROVSKA SALAMON, A., GROENENDAAL, F., VAN HAASTERT, I. C., RADEMAKER, K. J., BENDERS, M. J., KOOPMAN, C. & DE VRIES, L. S. 2014. Neuroimaging and neurodevelopmental outcome of preterm infants with a

periventricular haemorrhagic infarction located in the temporal or frontal lobe. *Dev Med Child Neurol,* 56**,** 547-55.
SORAISHAM, A. S., AMIN, H. J., AL-HINDI, M. Y., SINGHAL, N. & SAUVE, R. S. 2006. Does necrotising enterocolitis impact the neurodevelopmental and growth outcomes in preterm infants with birthweight ≤1250 g? *Journal of Paediatrics and Child Health,* 42**,** 499-504.
SPENCER, J. P., CORBETTA, D., BUCHANAN, P., CLEARFIELD, M., ULRICH, B., SCHÖNER, G. & SCHÖNER, G. 2006. Moving toward a grand theory of development: in memory of Esther Thelen. *Child Development,* 77**,** 1521-1538.
SPITTLE, A., ORTON, J., ANDERSON, P., BOYD, R. & DOYLE, L. 2015. Early developmental intervention programmes provided post hospital discharge to prevent motor and cognitive impairment in preterminfants (Review). *Cochrane Database of Systematic Reviews*.
SPITTLE AJ, B. N., DOYLE LW, BOYD RN, HUNT RW, BEAR M 2008. Quality of General Movements Is Related to White Matter Pathology in Very Preterm Infants. *Pediatrics,* 121**,** e1184 - 1189.
SPITTLE, A. J., DOYLE, L. W. & BOYD, R. N. 2008. A systematic review of the clinimetric properties of neuromotor assessments for preterm infants during the first year of life. *Developmental Medicine & Child Neurology,* 50**,** 254-266.
SPITTLE AJ, L. K., SPENCER-SMITH M, LOREFICE LE, ANDERSON PJ, DOYLE LW 2015. Accuracy of Two Motor Assessments during the First Year of Life in Preterm Infants for Predicting Motor Outcome at Preschool Age. *PLoS One,* 10**,** e0125854.
SPITTLE, A. J., SPENCER-SMITH, M. M., CHEONG, J. L., EELES, A. L., LEE, K. J., ANDERSON, P. J. & DOYLE, L. W. 2013. General movements in very preterm children and neurodevelopment at 2 and 4 years. *Pediatrics,* 132**,** e452-8.
SRIPADA, K., LØHAUGEN, G., C.,, EIKENES, L., BJØRLYKKE, K., M.,, HÅBERG, A., K.,, SKRANES, J. & RIMOL, L. M. 2015. Visual-motor deficits relate to altered gray and white matter in young adults born preterm with very low birth weight. *NeuroImage,* 109**,** 493-504.
STALNAKER, K. A. & POSKEY, G. A. 2016. Osteopenia of Prematurity: Does Physical Activity Improve Bone Mineralization in Preterm Infants? *Neonatal Network,* 35**,** 95-104.
STEER, P. 2005. The epidemiology of preterm labour. *BJOG: an International Journal of Obstetrics and Gynaecology,* 112**,** 1 - 3.
STEINLIN, M. 2007. The cerebellum in cognitive processes: Supporting studies in children. *The Cerebellum,* 6**,** 237 - 241.
STEPHENS, B. E., LIU, J., LESTER, B., LAGASSE, L., SHANKARAN, S., BADA, H., BAUER, C., DAS, A. & HIGGINS, R. 2010. Neurobehavioral Assessment Predicts Motor Outcome in Preterm Infants. *The Journal of Pediatrics,* 156**,** 366-371.
STOLL, B. J., HANSEN, N. I., BELL, E. F., WALSH, M. C., CARLO, W. A., SHANKARAN, S., LAPTOOK, A. R., SANCHEZ, P. J., VAN MEURS, K. P., WYCKOFF, M., DAS, A., HALE, E. C., BALL, M. B., NEWMAN, N. S., SCHIBLER, K., POINDEXTER, B. B., KENNEDY, K. A., COTTEN, C. M., WATTERBERG, K. L., D'ANGIO, C. T., DEMAURO, S. B., TRUOG, W. E., DEVASKAR, U., HIGGINS, R. D., EUNICE KENNEDY SHRIVER NATIONAL INSTITUTE OF CHILD, H. & HUMAN DEVELOPMENT NEONATAL RESEARCH, N. 2015. Trends in Care Practices, Morbidity, and Mortality of Extremely Preterm Neonates, 1993-2012. *JAMA,* 314**,** 1039-51.
STOLT, S., KORJA, R., MATOMAKI, J., LAPINLEIMU, H., HAATAJA, L. & LEHTONEN, L. 2014. Early relations between language development and the quality

of mother-child interaction in very-low-birth-weight children. *Early Hum Dev,* 90**,** 219-25.
STOODLEY, C. J. 2012. The Cerebellum and Cognition: Evidence from Functional Imaging Studies. *The Cerebellum,* 11**,** 352-365.
SWAMY, G., OUTBID, T. & SKJARVEN, R. 2008. Association of Preterm Birth With Long-term Survival, Reproduction and Next- generation Preterm Birth. *Journal of American medical Association,* 299**,** 1429 - 1436.
SWEENEY, J. K. & GUTIERREZ, T. 2002. Musculoskeletal Implications of Preterm Infant Positioning in the NICU. *Journal of Perinatal & Neonatal Nursing* 16**,** 58 - 70.
TAHERI, P. A., GOUDARZI, Z., SHARIAT, M., NARIMAN, S. & MATIN, E. N. 2018. The effect of a short course of moderate pressure sunflower oil massage on the weight gain velocity and length of NICU stay in preterm infants. *Infant Behavior and Development,* 50**,** 22-27.
TANIS, J. C., VAN BRAECKEL, K. N. J. A., KERSTJENS, J. M., BOCCA-TJEERTES, I. F. A., REIJNEVELD, S. A. & BOS, A. F. 2015. Functional Outcomes at Age 7 Years of Moderate Preterm and Full Term Children Born Small for Gestational Age. *The Journal of Pediatrics,* 166**,** 552-558.e1.
THELEN, E. 1989. The (re)discovery of motor development: Learning new things from an old field. *Developmental Psychology,* 25**,** 946-949.
THELEN, E. 1995. Motor development: A new synthesis. *Thelen, E. (1995). Motor development: A new synthesis. American Psychologist, 50(2), 79-95*.
THOMPSON, D. K., INDER, T. E., FAGGIAN, N., JOHNSTON, L., WARFIELD, S. K., ANDERSON, P. J., DOYLE, L. W. & EGAN, G. F. 2011. Characterization of the corpus callosum in very preterm and full-term infants utilizing MRI. *NeuroImage,* 55**,** 479-490.
TIEMAN, B. L., PALISANO, R. J. & SUTLIVE, A. C. 2005. Assessment of motor development and function in preschool children. *Ment Retard Dev Disabil Res Rev,* 11**,** 189-96.
TONG, V. T., ENGLAND, L. J., ROCKHILL, K. M. & D'ANGELO, D. V. 2017. Risks of Preterm Delivery and Small for Gestational Age Infants: Effects of Nondaily and Low-Intensity Daily Smoking During Pregnancy. *Paediatric and Perinatal Epidemiology***,** n/a-n/a.
TOSO, B. R. G. D. O., VIERA, C. S., VALTER, J. M., DELATORE, S. & BARRETO, G. M. S. 2015. Validation of newborn positioning protocol in Intensive Care Unit. *Revista Brasileira de Enfermagem,* 68**,** 1147-1153.
TREDGETT, S. 2015. *Learning through Movement in the Early Years,* Glasgow, Bell & Blain.
TSIMIS, M. E., JOHNSON, C. T., RAGHUNATHAN, R. S., NORTHINGTON, F. J., BURD, I. & GRAHAM, E. M. 2015. Risk Factors for Periventricular White Matter Injury in Very Low Birth Weight Neonates. *Am J Obstet Gynecol*.
UNAIDS 2017. South Africa Country Report 2017.
USTAD, T., EVENSEN, K. A. I., CAMPBELL, S. K., GIROLAMI, G. L., HELBOSTAD, J., JØRGENSEN, L., KAARESEN, P. I. & ØBERG, G. K. 2016. Early Parent-Administered Physical Therapy for Preterm Infants: A Randomized Controlled Trial. *Pediatrics,* 138.
VAIVRE-DOURET, L., ORIOT, D., BLOSSIER, P., PY, A., KASOLTER-PÉRÉ, M. & ZWANG, J. 2009. The effect of multimodal stimulation and cutaneous application of vegetable oils on neonatal development in preterm infants: a randomized controlled trial. *Child: Care Health & Development,* 35**,** 96-105.

VAN DER LUGT, N. M., SMITS-WINTJENS, V. E. H. J., VAN ZWIETEN, P. H. T. & WALTHER, F. J. 2010. Short and long term outcome of neonatal hyperglycemia in very preterm infants: a retrospective follow-up study. *BMC pediatrics,* 10**,** 52-52.
VAN HUS, J. W. P., JEUKENS-VISSER, M., KOLDEWIJN, K., HOLMAN, R., KOK, J. H., NOLLET, F. & VAN WASSENAER-LEEMHUIS, A. G. 2016. Early intervention leads to long-term developmental improvements in very preterm infants, especially infants with bronchopulmonary dysplasia. *Acta Paediatrica,* 105**,** 773-781.
VANDENBERG, K. A. 2007. Individualized developmental care for high risk newborns in the NICU: a practice guideline. *Early Hum Dev,* 83**,** 433-42.
VANDERVEEN, J. A., BASSLER, D., ROBERTSON, C. M. T. & KIRPALANI, H. 2009. Early interventions involving parents to improve neurodevelopmental outcomes of premature infants: a meta-analysis. *Journal Of Perinatology,* 29**,** 343.
VAUGHAN, C. L. 2003. Theories of bipedal walking: an odyssey. *Journal of Biomechanics,* 36**,** 513-523.
VENETSANOU, F. & KAMBAS, A. 2010. Environmental Factors Affecting Preschoolers' Motor Development. *Early Childhood Education Journal,* 37**,** 319-327.
VENTURA, ALISON K. & WOROBEY, J. 2013. Early Influences on the Development of Food Preferences. *Current Biology,* 23**,** R401-R408.
VERBRUGGEN, S. W., LOO, J. H. W., HAYAT, T. T. A., HAJNAL, J. V., RUTHERFORD, M. A., PHILLIPS, A. T. M. & NOWLAN, N. C. 2016. Modeling the biomechanics of fetal movements. *Biomechanics and Modeling in Mechanobiology,* 15**,** 995-1004.
VERLATO, G., SIMONATO, M., GIAMBELLUCA, S., FANTINATO, M., CORREANI, A., CAVICCHIOLO, M. E., PRIANTE, E., CARNIELLI, V. & COGO, P. 2018. Surfactant Components and Tracheal Aspirate Inflammatory Markers in Preterm Infants with Respiratory Distress Syndrome. *The Journal of Pediatrics.*
VICKERS, J. N. 2011. Mind over muscle: the role of gaze control, spatial cognition, and the quiet eye in motor expertise. *Cognitive Processing,* 12**,** 219-222.
VIGNOCHI, C. M., MIURA, E. & CANANI, L. H. 2008. Effects of motor physical therapy on bone mineralization in premature infants: a randomized controlled study. *J Perinatol,* 28**,** 624-31.
VIHOLAINEN, H., AHONEN, T., CANTELL, M., TOLVANEN, A. & LYYTINEN, H. 2006. The Early Motor Milestones in Infancy and Later Motor Skills in Toddlers. *Physical & Occupational Therapy In Pediatrics,* 26**,** 91-113.
VINCER, M. J., CAKE, H., GRAVEN, M., DODDS, L., MCHUGH, S. & FRABONI, T. 2005. A population-based study to determine the performance of the Cognitive Adaptive Test/Clinical Linguistic and Auditory Milestone Scale to Predict the Mental Developmental Index at 18 Months on the Bayley Scales of Infant Development-II in very preterm infants. *Pediatrics,* 116**,** e864-7.
VLIEGENTHART, R. J. S., ONLAND, W., VAN WASSENAER-LEEMHUIS, A. G., DE JAEGERE, A. P. M., AARNOUDSE-MOENS, C. S. H. & VAN KAAM, A. H. 2017. Restricted Ventilation Associated with Reduced Neurodevelopmental Impairment in Preterm Infants. *Neonatology,* 112**,** 172-179.
VOHR, B. 2013. Long-term outcomes of moderately preterm, late preterm, and early term infants. *Clin Perinatol,* 40.
VOLPE, J. J. 2009. Brain injury in premature infants: a complex amalgam of destructive and developmental disturbances. *The Lancet Neurology,* 8**,** 110-124.
VON ELM, E., ALTMAN, D. G., EGGER, M., POCOCK, S. J., GØTZSCHE, P. C., VANDENBROUCKE, J. P. & INITIATIVE, F. T. S. 2007. The Strengthening the

Reporting of Observational Studies in Epidemiology (STROBE) Statement: Guidelines for Reporting Observational Studies. *Epidemiology,* 18**,** 800-804.
VRACHNIS, N., VITORATOS, N., ILIODROMITI, Z., SIFAKIS, S., DELIGEOROGLOU, E. & CREATSAS, G. 2010. Intrauterine inflammation and preterm delivery. *Annals of the New York Academy of Sciences,* 1205**,** 118-122.
WADHWA, P. D., ENTRINGER, S., BUSS, C. & LU, M. C. 2011. The Contribution of Maternal Stress to Preterm Birth: Issues and Considerations. *Clinics in Perinatology,* 38**,** 351-384.
WAITZMAN, K. A. 2007. The Importance of Positioning the Near-term Infant for Sleep, Play, and Development. *Newborn and Infant Nursing Reviews,* 7**,** 76-81.
WALSH, M. C., MORRIS, B. H., WRAGE, L. A., VOHR, B. R., POOLE, W. K., TYSON, J. E., WRIGHT, L. L., EHRENKRANZ, R. A., STOLL, B. J. & FANAROFF, A. A. 2005. Extremely Low Birthweight Neonates with Protracted Ventilation: Mortality and 18-Month Neurodevelopmental Outcomes. *The Journal of Pediatrics,* 146**,** 798-804.
WANG, L., HE, J. L. & ZHANG, X. H. 2013. The efficacy of massage on preterm infants: a meta-analysis. *Am J Perinatol,* 30.
WASSENBERG, R., FERON, F. J. M., KESSELS, A. G. H., HENDRIKSEN, J. G. M., KALFF, A. C., KROES, M., HURKS, P. P. M., BEEREN, M., JOLLES, J. & VLES, J. S. H. 2005. Relation Between Cognitive and Motor Performance in 5- to 6-Year-Old Children: Results From a Large-Scale Cross-Sectional Study. *Child Development,* 76**,** 1092-1103.
WAYTZ, A., GRAY, K., EPLEY, N. & WEGNER, D. M. 2010. Causes and consequences of mind perception. *Trends in Cognitive Sciences,* 14**,** 383-388.
WECK, R. L., PAULOSE, T. & FLAWS, J. A. 2008. Impact of Environmental Factors and Poverty on Pregnancy Outcomes. *Clinical obstetrics and gynecology,* 51**,** 349 - 359.
WEISS-CROFT, L. J. & BALDEWEG, T. 2015. Maturation of language networks in children: A systematic review of 22 years of functional MRI. *NeuroImage,* 123**,** 269-281.
WESTCOTT SL, L. L., RICHARDSON PK 1997. Evaluation of Postural Stability in Children: Current Theories and Assessment Tools. *Physical Therapy,* 77**,** 629-645.
WESTERHAUSEN, R., FRIESEN, C.-M., ROHANI, D. A., KROGSRUD, S. K., TAMNES, C. K., SKRANES, J. S., HÅBERG, A. K., FJELL, A. M. & WALHOVD, K. B. 2018. The corpus callosum as anatomical marker of intelligence? A critical examination in a large-scale developmental study. *Brain Structure and Function,* 223**,** 285-296.
WHEELER, K. I., KLINGENBERG, C., MORLEY, C. J. & DAVIS, P. G. 2011. Volume-Targeted versus Pressure-Limited Ventilation for Preterm Infants: A Systematic Review and Meta-Analysis. *Neonatology,* 100**,** 219-227.
WHELAN, C. T. 2014. Improvement in prematurity outcome: A chiropractic case report. *JOURNAL OF CLINICAL CHIROPRACTIC PEDIATRICS***,** 1160.
WOODS, P. L., RIEGER, I., WOCADLO, C. & GORDON, A. 2014. Predicting the outcome of specific language impairment at five years of age through early developmental assessment in preterm infants. *Early Human Development,* 90**,** 613-619.
WORLD HEALTH ORGANIZATION. 2017. *Preterm Birth Fact Sheets* [Online]. Available: http://www.who.int/mediacentre/factsheets/fs363/en/ [Accessed 22/03/2018 2018].
WOYTHALER, M., MCCORMICK, M. C., MAO, W. Y. & SMITH, V. C. 2015. Late Preterm Infants and Neurodevelopmental Outcomes at Kindergarten. *Pediatrics,* 136**,** 424-31.
WU, C. & SUN, D. 2015. GABA receptors in brain development, function, and injury. *Metabolic brain disease,* 30**,** 367-379.

WU, H. G., MIYAMOTO, Y. R., CASTRO, L. N. G., ÖLVECZKY, B. P. & SMITH, M. A. 2014a. Temporal structure of motor variability is dynamically regulated and predicts motor learning ability. *Nature neuroscience,* 17**,** 312-321.

WU, Y.-C., LENG, C.-H., HSIEH, W.-S., HSU, C.-H., CHEN, W. J., GAU, S. S.-F., CHIU, N.-C., YANG, M.-C., LI-JUNG, F., HSU, H.-C., YU, Y.-T., WU, Y.-T., CHEN, L.-C. & JENG, S.-F. 2014b. A randomized controlled trial of clinic-based and home-based interventions in comparison with usual care for preterm infants: Effects and mediators. *Research in Developmental Disabilities,* 35**,** 2384-2393.

YU, Q., OUYANG, A., CHALAK, L., JEON, T., CHIA, J., MISHRA, V., SIVARAJAN, M., JACKSON, G., NANCY, LIU, S. & HUANG, H. 2016. Structural Development of Human Fetal and Preterm Brain Cortical Plate Based on Population-Averaged Templates. *Cerebral Cortex,* 26**,** 4381–4391.

ZAFEIRIOU, D. I. 2004. Primitive reflexes and postural reactions in the neurodevelopmental examination. *Pediatric Neurology,* 31**,** 1-8.

ZAGHLOUL, N., PATEL, H. & AHMED, M. N. 2017. A model of Periventricular Leukomalacia (PVL) in neonate mice with histopathological and neurodevelopmental outcomes mimicking human PVL in neonates. *PLoS ONE,* 12**,** e0175438.

ZAREM, C., CRAPNELL, T., TILTGES, L., MADLINGER, L., REYNOLDS, L., LUKAS, K. & PINEDA, R. 2013. Neonatal Nurses' and Therapists' Perceptions of Positioning for Preterm Infants in the Neonatal Intensive Care Unit. *Neonatal network : NN,* 32**,** 110-116.

ZEITLIN J, SAUREL-CUBIZOLLES M.J, DE MOUZON J, RIVERA L, ANCEL P, BLONDEL B & M;, K. 2002. Fetal sex and preterm birth: are males at greater risk? *Human Reproduction,* 17**,** 2762 - 2768.

ZEKA, A., MELLY, S. J. & SCHWARTZ, J. 2008. The effects of socioeconomic status and indices of physical environment on reduced birth weight and preterm births in Eastern Massachusetts. *Environ Health,* 7**,** 60.

ZWICKER, J. G. & HARRIS, S. R. 2009. A reflection on motor learning theory in pediatric occupational therapy practice. *The Canadian Journal of Occupational Therapy,* 76**,** 29-37.

ZWICKER, J. G., MISSIUNA, C., HARRIS, S. R. & BOYD, L. A. 2012. Developmental coordination disorder: A review and update. *European Journal of Paediatric Neurology,* 16**,** 573-581.

APPENDIX I: Ethical Clearance

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG
Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Diana Brown

CLEARANCE CERTIFICATE **M120817**

PROJECT The Effect of An In-Patient Physiotherapy Programme in the Neonatal Intensive Care Unit on Long-Term Development Outcomes of Pre-Term Infants

INVESTIGATORS Diana Brown.

DEPARTMENT Department of Physiotherapy

DATE CONSIDERED 31/08/2012

DECISION OF THE COMMITTEE* Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 09/10/2012 **CHAIRPERSON** .....
(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable
cc: Supervisor : Dr Joanne Potterton

DECLARATION OF INVESTIGATOR(S)
To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10004, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES...

APPENDIX II: Informed consent

INFORMATION DOCUMENT

The effect of an in-patient physiotherapy programme in the Neonatal Intensive Care Unit on long-term developmental outcomes on pre-term infants

My name is Diana Brown, and I am a Physiotherapy PhD student at the University of the Witwatersrand. I am doing a study to investigate the effectiveness of a certain in-patient physiotherapy programme on premature infants on their long-term developmental outcomes. Other research that has been done has shown that prematurity may affect development. This information will help to implement a programme that is effective for development as well as cost for government institutions.

Invitation to participate

I would like your permission to include your child in this study, as he/she was born prematurely

What is involved in the study?

If your child is in the intervention group they will receive the programme whilst he/she is on hospital and is stable. When your child is term age, six, 12 and 18 months of age he/she will be assessed by the research assistant, using a standardised test of development. The test looks at all areas of development and will be fun for your child, as it involves toys and games. The test takes on average an hour to administer. The procedure will be done in a physiotherapy practice.

Risks

There are no risks to being involved in the study.

Benefits

The results of the assessment will be discussed with you. If any developmental delay is picked up your child will be referred to the appropriate person.

Participation is voluntary

You may refuse permission for your child to be part of the study, and your child's treatment at the clinic will not be affected in any way.

Confidentiality

All your personal information will be kept confidential. No names will be used, and the researcher will be the only person with access to your information.

Contact details:

For further information please feel free to contact Diana Brown on 0845854044 or dianacoetzer@gmail.com. Contact detail of the ethics committee is Professor Peter Cleaton-Jones Peter.Cleaton-Jones@wits.ac.za 011 717-1234.

INFORMED CONSENT

I, _____, parent/ guardian of _____ have read the information sheet attached and agree to allow my child to participate in the research study.

I agree for my child's information to be used I the study. I am aware of the fact that I may withdraw from the study at any time and that all information will be kept confidential.

_____	_____
Parent/Guardian	Witness
_____	_____
Date	Date

APPENDIX III: Demographic and Clinical Information Sheet

Information Sheet

Patient Number:

Gestation		
Birth weight		
Length		
Head circumference		
Sex		
Multiples		
Antenatal Steroid use		
APGAR Scores		
Artificial Ventilation		
Length of artificial ventilation		
Maternal Age		
Maternal Education Level		
Surfactant		
Oxygen Therapy		
NEC		
IVH		
PVL		
Co-morbidity factors		
Surgery		
Additional Diagnosis		
Ventricular Dilatation		
Cranial US	Normal	Abnormal
Retinopathy of prematurity		
Number of previous pregnancies?		
Outcome of previous pregnancies:		
Problems during pregnancies?		

Appendix IV Letters of Permission from Participating Hospitals

/PHYSICAL ADDRESS
Amplifier Road
Radiokop Ext 13
Roodepoort
1724

10 June 2012

To whom it may concern
This is to certify that Mrs Diana Coetzer has been granted permission for this study to be conducted at the Life Wilgeheuwel Hospital pending ethical clearance.

Yours sincerely

Jacques De Klerk
Hospital Manager

PHYSICAL ADDRESS
9 Burger Street
Krugersdorp
1740
Tel: +27 (0) 11 951 0200
Fax: +27 (0)11 660 1882

05 June 2012

To whom it may concern
This is to certify that Mrs Diana Coetzer has been granted permission for this study to be conducted at the Nectare Krugersdorp Hospital pending ethical clearance.

Yours sincerely

Sr Ayers
NICU Unit Manager

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