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DEVELOPMENTAL OUTCOMES FOR INFANTS WITH HYPOXIC ISCHAEMIC ENCEPHALOPATHY (HIE) WHO HAVE AND HAVE NOT UNDERGONE WHOLE-BODY HYPOTHERMIA.

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Dissertation submitted to the Faculty of Health Sciences, School of Therapeutic Sciences, University of the Witwatersrand, Johannesburg, in fulfilment of the requirements for the degree of

Master of Science in Occupational Therapy

Johannesburg, 2016

DECLARATION

I, Bianca Chantelle Pereira declare that this research report is my own work. It is being submitted for the degree of Master of Science in Occupational Therapy at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.



..(Signature of candidate)

13th day of June, 2016.

DEDICATION

My husband,

for his unwavering support, love and patience.

ABSTRACT

This study aimed to determine the developmental outcomes for infants between the ages of five and 16 months who had and had not received induced hypothermia at Chris Hani Baragwanath Academic Hospital (CHBAH). Forty-three infants diagnosed with HIE II and HIE III were assessed using the Bayley Scales of Infant and Toddler Development – III (Bayley-III) at baseline and were reassessed three to nine months later having received intervention from the transdisciplinary rehabilitation team at CHBAH.

The majority of infants (78.3%) who had and had not received induced hypothermia both presented with typical developmental outcomes at baseline with 21.7% having moderate to severe dysfunction. On reassessment (31 infants), the developmental outcomes deteriorated for both groups; with more infants in the group which had received hypothermia falling into the at risk category. In spite of this, the majority of infants (in both groups) that were reassessed were overall developmentally on par.

This study highlights the importance of on-going monitoring of infants with HIE, receiving home programmes and the need for therapeutic intervention after the age of one year with a focus on specific developmental issues. Standardized assessments are essential to facilitate more precise and effective intervention programmes.

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OPERATIONAL DEFINITIONS:

- **Occupational therapy in Early Intervention:** Occupational therapists who are responsible for promoting the engagement and function of infants as well as toddlers and their families in occupational performance areas of rest and sleep, activities of daily living, social engagement, education and play[1].
- **Neurodevelopmental disorders (NDDs):** Disabilities in the functioning of the brain that affect a child's behaviour, memory or ability to learn e.g. dyslexia, mental retardation, autism, learning deficits and attention deficit hyperactivity disorder (ADHD)[2].
- **Neonatal Encephalopathy (NE):** 'Clinically defined syndrome of disturbed neurological function in the earliest days of life in the full-term infant, manifested by difficulty with initiating and maintaining respiration, depression of tone and reflexes, subnormal level of consciousness and often seizures[3].
- **Hypoxic Ischaemic Encephalopathy (HIE):** An acute, evolving type of neonatal encephalopathy, which is characterised by brain ischemia, as well as hypoxia that occurs either intra or antepartum[4].
- **Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III):** An assessment tool developed by Nancy Bayley which is used to measure, identify and assess development in children. It is a comprehensive manner of identifying developmental issues or delays in children from the ages of one month to 42 months to aid health professionals in early identification to ensure early intervention is carried out[5].
- **Whole body induced hypothermia:** Intervention implemented by turning reducing a neonates temperature in attempts to reduce mortality without increasing neurological deficits and to decrease long-term neurodevelopmental disability[6].

ABBREVIATIONS

AAP	American Academy of Paediatrics
ABAS-II	Adaptive Behaviour Assessment System, Second Edition
ACOG	American College of Obstetricians and Gynaecologists
ARICO	Association for Research in Infant and Child Development
Bayley-III	Bayley Scales of Infant and Toddler Development, Third Edition
BD	base deficits
BSID-II	Bayley Scales of Infant Development, Second Edition
CHBAH	Chris Hani Baragwanath Academic Hospital
CP	cerebral palsy
EEG	electroencephalogram
GAC	General Adaptive Composite
GMDS – ER	Griffiths Mental Development Scales – Extended Revision
HIE	hypoxic ischemic encephalopathy
HIV	Human Immunodeficiency Virus
ICPTF	International Cerebral Palsy Task Force
mEq/L	milliequivalents per litre
NDDs	neurodevelopmental disorders
NDT	neurodevelopmental therapy
NE	neonatal encephalopathy
NICU	neonatal intensive care units
NMDA	N-methyl D-aspartate
NNFUC	Neonatal Follow Up Clinics
NNJ	neonatal jaundice
NOS	Nitric oxide synthase

PCR	polymerase chain reaction
PDMS-II	Peabody Developmental Motor Scales, Second Edition
PMTCT	Prevention of Mother-To-Child Transmission
RDP	Reconstruction and Development Programme
RVD	retroviral disease
TAGA	term appropriate gestational age
TICU	transitional intensive care unit
TOBY	Total Body Hypothermia for Neonatal Encephalopathy
UK	United Kingdom
USA	United States of America

CHAPTER 1: INTRODUCTION

1.1 Introduction to the study

Hypoxic ischemic encephalopathy (HIE) is one of the main causes of mortality and morbidity of neonates throughout the world. Worldwide, the incidence has been estimated at 3.0 per 1000 live births with the incidence in developed countries being lower at 1.5 per 1000 live births and 4.6 per 1000 live births in developing countries[7, 8]. In South Africa, in 2009, the incidence was 8.3/1000 live births[6, 9, 4, 10]. In a South African study it was evident that the morbidity and mortality for HIE in South African resource-limited settings i.e. Chris Hani Baragwanath Academic Hospital (CHBAH) was high[11].

It is important that infants presenting with HIE are detected and diagnosed early and that the best treatment is offered to them to achieve the best outcomes in these children. Funding needs to be allocated appropriately to the most vital areas of treatment to achieve these outcomes. Buchmann and Velaphi, indicated in their study that a vital area is that of a multidisciplinary team approach in the management of the far-reaching and long-term concerns and consequences that HIE has on infants as well as the factors affecting the outcome of this condition are to be addressed. Health care practitioners need to identify the areas of suboptimal care as well as administration related and family or patient-related problems so that these can be addressed to achieve the best outcome for infants with HIE[12].

Recently, in settings which have a neonatal intensive care unit, therapeutic whole-body induced hypothermia is a strategy which has been initiated to reduce both death or severe disability in those neonates who are diagnosed with moderate HIE II or severe HIE (HIEIII)[13]. It is imperative that these neonates be admitted and have induced hypothermia within the first six hours of life (window of opportunity)[10]. Limitations throughout the world, but particularly in resource-limited settings, mean that neonates are often admitted to neonatal intensive care units (NICUs) after six hours of age as well as that there are insufficient resources for all infants to be cooled. Consequently, the severity of HIE amongst infants treated in resource constrained settings may be higher [6, 14, 15, 16].

There is no evidence to support the efficacy or safety of induced hypothermia in resource-limited settings where there is no NICU. In South Africa there are, however, public institutions, which have adequate NICUs where induced hypothermia could be effective in spite of the limitations at these institutions. It is therefore important to develop an evidence-based standard protocol for the implementation of therapeutic hypothermia to be used in these NICUs. This can only be done with continued research on hypothermia for HIE. It is imperative that infants who are at risk of HIE are identified timeously through the use of specific criteria for diagnosis, and a standardized neurological examination for evaluation of HIE. There also needs to be a coordinated system in conjunction with primary and secondary health care facilities to ensure that infants are transferred appropriately so induced hypothermia can be made available even for infants who are born at various facilities without a NICU.

It is essential for the infants to be followed up throughout their childhood and for standardised neurodevelopmental assessments to be carried out to determine if the infant or child needs to be in a therapeutic program to facilitate development. In order to ensure that the services offered to these children provide the best outcomes, these services need to be closely and thoroughly monitored to improve the quality of services provided. A multidisciplinary approach based on the understanding of child development should be provided to assist the parents with educational home programmes[17].

1.2 Statement of the problem

Many studies have reported that induced hypothermia reduced mortality without increasing neurological deficits and that decreased long term neurodevelopmental disability was found in infants with HIE at the age of 18 months[6, 9, 14, 18, 19.] Understanding the extent of this effect and the specific areas of development that are impacted by induced hypothermia still require further research. At Chris Hani Baragwanath Academic Hospital the induced whole-body hypothermia programme has been in place since October 2011 and neonates are selected for this programme based on specific selection criteria. At present, there are not enough resources available for all infants diagnosed with HIE so it is important to determine what effects the induced hypothermia is having on developmental outcomes.

No studies on transdisciplinary early intervention therapeutic programmes on children with neurological impairment have been published, however, various disciplines have reported effective early intervention for improving motor performance, integrating sensory-motor experiences, quality of eye/hand function, sensation and perception[20-22]. Understanding developmental outcomes in infants and children with HIE provides a platform for developing and evaluating therapeutic programmes.

1.3 Purpose of the study

This study investigated the developmental outcomes of infants with HIE as well as the differences in these for infants who received whole-body induced hypothermia versus those who did not. Cognition, language, motor, socio-emotional and adaptive behaviour areas of development will be assessed in infants with HIE who did and did not receive induced hypothermia. Infants were assessed before they were 12 months old and reassessed three to nine months later. These infants all received a transdisciplinary early intervention therapy programme administered by an occupational therapist, speech therapist or a physiotherapist at CHBAH. This programme focused on assessment, a basic home programme as well as monitoring of development. If, on assessment, it was determined that these infants require more specific intervention they would be referred to the relevant clinic.

1.4 Aims and objectives of the study:

This study aimed to determine the developmental outcomes of infants with HIE who had received induced hypothermia and those who had not and were attending a programme provided by the transdisciplinary rehabilitation team over a period of time. The developmental outcomes of infants with HIE II in comparison to those with HIE III were also determined.

1.4.1 Objectives of the study:

The study was conducted to determine the following:

- To determine the developmental outcomes of infants who had received induced hypothermia and those who had not according to the Bayley Scales of Infant and Toddler Development – Third Edition.
- To determine the change in developmental outcomes of infants who have received induced hypothermia attending transdisciplinary rehabilitation at CHBAH after a period of three to nine months.
- To determine and compare the developmental outcomes of infants with HIE II and HIE III.

1.5 Justification of the study

It is important to understand the developmental outcomes of infants with HIE in infants who have and have not received induced hypothermia. This will assist in determining the effects of the whole body induced hypothermia program for infants with HIE treated at CHBAH so that further resources for the program can be motivated for. The research allows us to understand the areas of development that require more focus in transdisciplinary early intervention programs. The aim is for the therapists working within this program to be aware of the areas of development that require targeting as well as the effectiveness and appropriateness of their therapy.

CHAPTER 2: LITERATURE REVIEW

2.1 Introduction

This literature review serves to describe birth asphyxia and hypoxic ischemia and is extended to explain hypoxic ischemic encephalopathy; the pathophysiology, signs and symptoms, risk factors as well as the implications of this condition. Hypothermia, the pathophysiology of hypothermia as a treatment technique as well as the administration and effectiveness of this technique is reviewed. Neurodevelopmental disability secondary to birth asphyxia is considered, as well as, all components of normal development. The role of the occupational therapist as part of a transdisciplinary team is highlighted with specific information on various approaches used to treat children with neurodevelopmental disability.

The following databases were searched for literature – PubMed, Sciencedirect, Springer, Elsevier, EBSCO, JSTOR, Wiley and Omics online.

2.2 Perinatal Asphyxia

A neonate's developing brain is known to be susceptible to adverse events i.e. neonatal jaundice, maternal infections and physical trauma during delivery as well as labour.[23] Babies have adapted however in order to withstand a lack of oxygen for longer periods than adults, since foetal haemoglobin has a higher affinity for oxygen than adult haemoglobin. It has been commonly hypothesised that a baby's first breath is stimulated by the clamping of the umbilical cord due to the neonate changing from fluid-filled lungs to air filled lungs. This may result in hypoxia before the first breath is taken but the neonate can withstand a period of asphyxia during which circulation continues without harm[24]. In this case, the physiological process, common to mammals, protects vital organs. Outcomes from hypoxia are therefore related to the length of time that it took the process to take place as well as the degree of asphyxiation[25].

Halloran et al (2009), in a study conducted in eight African countries, described how birth asphyxia was found to cause 23% of neonatal mortalities, making it the leading cause of infant death on this continent[18]. In South Africa, although Kali et al. (2015)

found only a 11% mortality rate in their study [26], of those infants who survived, the reported morbidity was 77% for mild to moderate neurological disability due to hypoxia. This morbidity and mortality is similar to findings from other low and middle-income countries[27]. The neonatal brain can be more vulnerable to brain injury with precursors such as pre exposure to hypoxia. One of the most common causes of neonatal brain injury is hypoxic-ischemia (HI)[28].

2.2.1 Hypoxic Ischemia (HI)

Neonatal brain injury is an evolving process. It begins with the primary insult, this can include oxygen free radicals, calcium inflow, nitric oxide formation or excitatory neurotoxicity[29] and will continue on into the recovery period (reperfusion phase) of the injury. The primary mechanisms that underlie the damaging effects of hypoxic-ischemia include both primary apnoea as well as terminal apnoea. In primary apnoea an infant will fail to inflate their lungs with air in an attempt to breathe. This occurs when the placental oxygen supply has been interrupted. The reduction in oxygen content to the perfusing blood and poor perfusion of the brain due to an interruption of placental blood flow is often referred to as severe foetal acidaemia (umbilical arterial pH of < 7.00) or perinatal asphyxia[23, 30, 31].

2.2.1.1 Hypoxic Ischemia Pathophysiology – Primary Phase

There are two phases of hypoxic ischemia that are responsible for neuronal cell death. The primary phase begins at a cellular level where it is evident that the decreased oxygen delivery and cerebral blood flow start a cascade of damaging biochemical events. Oxidative phosphorylation occurs due to the oxygen depletion, which results in a switch to anaerobic metabolism. Anaerobic metabolism is an energy-inefficient state, which results in an accumulation of lactic acid; the inability to maintain cellular functions and rapid depletion of adenosine triphosphate (ATP). With the accumulation of calcium, water and sodium, the trans cellular ion-pump fails. The depolarization of the membrane will release glutamate (excitatory neurotransmitter) into the axon terminal[29, 32, 33].

Glutamate activates the cell surface receptors that create an inflow of calcium and sodium into the postsynaptic neurons. With the influx of intracellular calcium, lipases

are activated, which accumulate free fatty acids into the cytoplasm. The fatty acids go through the process of peroxidation through oxygen free radicals. This accumulation induces the production of free radicals in selected neurons; which is caused by a number of processes. These free radicals will make their way into the adjacent cells, which are at risk of nitric-oxide (free radical) toxicity (Figure 2.1)[28, 29, 33].

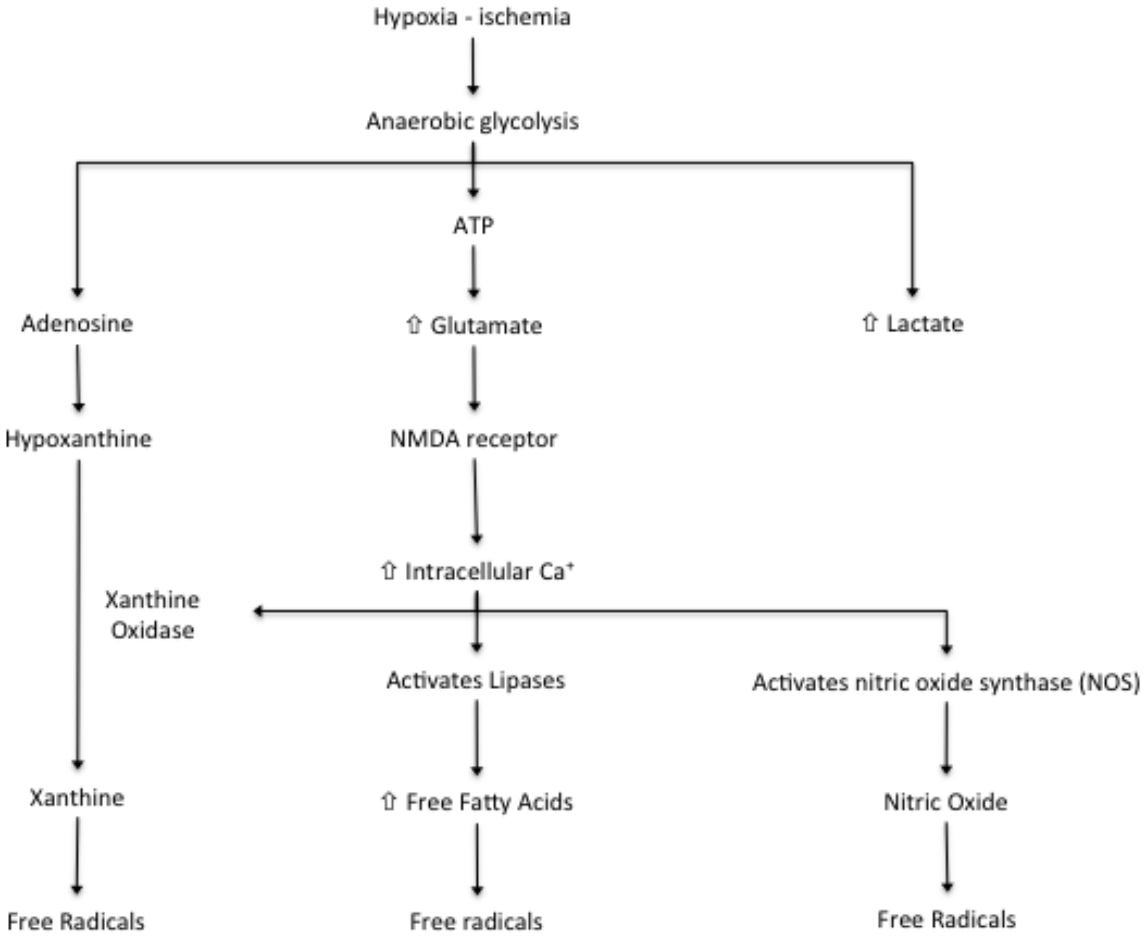

Figure 2.1 Potential pathways for brain injury after hypoxia-ischemia. (Perlman JM. Summary proceedings from the neurology group on Hypoxic-ischemic encephalopathy. Pediatrics. 2006; 117 (3): 29).

The combined effects of acidosis, intracellular calcium accumulation, cellular energy failure, lipid peroxidation, glutamate release and nitric oxide neurotoxicity disturb the fundamental components of the cell[13]. In conjunction with this, sustained hypoxia impairs activation of genes (i.e. hypoxia inducible factor) and their target molecules, decreasing translation and transcription as well as gene expression. Ultimately this will all lead to neuronal cell death[13, 32].

2.2.1.2 Hypoxic Ischemia Pathophysiology – Secondary Phase

The secondary phase injury is due to reperfusion injury. After resuscitation, which is generally carried out either in utero or postnatally in the delivery room, perfusion and oxygenation are restored. This recovery phase returns both the cellular pH and concentrations of phosphorous metabolites to baseline. The concern however is that there is a second phase of injury, which occurs after six to 48 hours post resuscitation, where cerebral energy failure recurs. This second phase occurs when re-oxygenation results in a secondary insult. Re-oxygenation is essential for an infant's survival, but it includes uneven metabolism in less privileged organs (e.g. kidneys and muscles) and metabolically privileged organs (e.g. brain, heart and adrenal medulla). The secondary phase of injury involves multiple mechanisms[6, 28, 32, 33].

During re-oxygenation the extracellular glutamate level increases, enhancing the activation of potassium and sodium ATPase that increases the ATP consumption further. Further mechanisms include mitochondrial dysfunction, secondary to an extension of the primary insult reactions, for example excitatory neurotoxicity, nitric-oxide formation, calcium influx and oxygen free radicals. Additionally, there is a suggestion through more recent evidence that endogenous and circulatory inflammatory cells/mediators contribute to on-going neonatal brain injury[13, 28, 32].

If the HI results in brain damage within 12 to 36 hours after birth, it leads to a type of neonatal encephalopathy known as hypoxic-ischemic encephalopathy (HIE) [6, 7, 14, 34].

2.3 Assessing the Infant for Hypoxic Ischemic Encephalopathy

Hypoxic Ischemic Encephalopathy has a higher incidence in developing, low-resourced settings[35, 36]. It is best understood by breaking down the name, hypoxic meaning caused by a lack of oxygen; ischemia meaning to be caused by reduced blood flow and encephalopathy meaning that it is a disease affecting the functioning of the brain[25].

It is often difficult for a neonatologist to distinguish whether or not hypoxic ischemic encephalopathy has occurred intrapartum or antepartum or if it is related to an underlying congenital abnormality[6, 28, 37]. In a study by Badawi et al (1998) however,

70% of cases found no evidence of adverse intrapartum events. Intrapartum risk factors include maternal pyrexia as well as acute events such as fetal haemorrhage, neonatal hypoglycemia or rhesus disease for hypoxic ischemic encephalopathy[38]. In a study done in Cape Town, South Africa by Fawcus (2004), it was evident that prolonged second stage deliveries, sub standard care as well as post term pregnancy were significant risk factors for hypoxic ischemic encephalopathy in a resource limited setting[39].

Research has also found evidence that emergency caesarean sections as well as assisted vaginal deliveries have an increased risk of HIE whereas elective caesarean sections have been associated with less risk for HIE[4, 28, 37].

Pre-conception and antepartum risk factors for hypoxic ischemic encephalopathy include family history of seizures or other neurological diseases, socioeconomic status, severe pre-eclampsia, maternal thyroid disease, bleeding in pregnancy, conception after infertility treatment, presence of an abnormal placenta, post maturity (birth after full term period), viral illnesses and intrauterine growth restriction[40]. Hypoxic Ischaemic Encephalopathy can also occur post natally as a result of a prenatal disorder such as persistent pulmonary hypertension[4].

Badawi et al (1998) reported that 69% of risk factors were due to antepartum factors related to maternal health as described above. Furthermore 25% were antepartum and intrapartum risk factors and only 4% were related to intrapartum hypoxia and 2% were of unknown risk factors[40] (Figure 2.2). A 2007 study by Palsdottir K found that risk factors included meconium aspiration (50%), abnormal cardiotocogram (CTG) (66% and 79% in HIE), umbilical cord wrapping around the infant's neck (41%) emergency caesarean section (19.7%), forceps assisted delivery (6.3%) and vacuum assisted delivery (22%)[37].

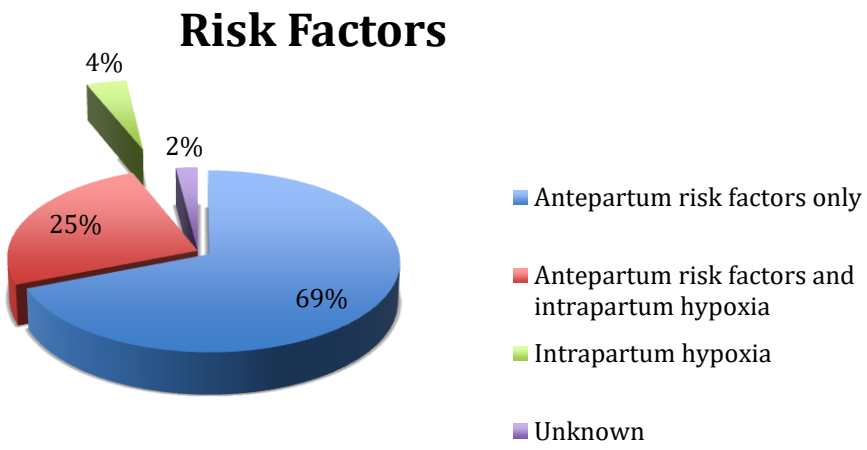

Figure 2.2 Distribution of risk factors for newborn encephalopathy. Hankins. Neonatal Encephalopathy and Cerebral Palsy. Obstet Gynecol. 2003. (Originally from the BMJ Publishing Group. Badawi N, Kurinczuk JJ, Keogh JM, Alessandri LM, O'Sullivan F, Burton PR, et al. Intrapartum risk factors for newborn encephalopathy: The Western Australian case control study. BMJ. 1998; 317: 1554–8).

Hypoxic ischemic encephalopathy symptoms in the neonate include: epileptic activity on electroencephalogram (EEG), seizures, poor feeding, sluggish or absent neonatal reflexes, occasional apnea, blood pressure and heart rate irregularities, irregular breathing, hypotonia and a depressed level of consciousness that typically lasts from seven to 14 days[14]. It is difficult to determine the extent and duration of the insult to the neonate's brain but an attempt is made to determine the prognosis as to understand the infant' s long-term disability[23, 1]. It is also vital to identify the infants that are at risk to ensure that an intervention is implemented as early as possible[30].

The International Cerebral Palsy Task Force (ICPTF) as well as the American College of Obstetricians and Gynaecologists (ACOG) and the American Academy of Pediatrics (AAP) have criteria for diagnosing HIE (Table 2.1). However, in a resource-limited setting this is not always a possibility. If these strict criteria are used, the actual incidence in settings such as these may be underestimated[36].

Table 2.1 Criteria for diagnosing intrapartal asphyxia as a cause of brain injury.[41]

American Academy of Pediatrics / American College of Obstetricians and Gynecologists (1996)	International Cerebral Palsy Task Force (ICTF) (1999)	American Academy of Pediatrics American College of Obstetricians and Gynecologists (2002)
pH < 7.0	pH < 7.0; BD ≥ 12 mmol/L (neonatal blood sampling)	pH < 7.0; BD ≥ 12 mmol/L (umbilical or neonatal blood sampling)
APGAR ≤ 3 at 5 minutes	APGAR < 6 at 5 minutes	APGAR ≤ 3 at 5 minutes
	Sentinel event/abrupt foetal heart rate change	Sentinel event/abrupt foetal heart rate change
Neonatal encephalopathy (NE)	NE II - III	NE II - III
Multi-organ dysfunction	Multi-organ failure	Multi-organ failure within 72 hours
	Cerebral palsy (CP)	CP and exclusion of other causes of brain injury
	Imaging evidence	Imaging evidence

Signs that place infants at risk and that are considered in identifying possible HIE include extended low Apgar scores[9, 13]. Other occurrences that place an infant at risk for HIE include unexpected events occurring during labour such as foetal heart rate abnormality. Evidence of severe foetal academia (cord umbilical artery pH <7.00 and/or base deficit (BD) of ≥16 milliequivalents per litre [mEq/L]), and the need for resuscitation through chest compression with or without adrenaline or through intubation are also considered risk factors[30].

These findings along with the examination for abnormal cerebral function and/or abnormal neurologic function through an electroencephalogram (EEG) give a good idea of the presence and extent as well as the duration of the hypoxic insult[13].

In 1976 Sarnat and Sarnat developed a grading system for HIE by staging the degree of encephalopathy[3]. They based this grading system on EEG results and clinical

symptoms. The clinical symptoms include depression of reflexes, whether or not there was difficulty in the infant with initiating or maintaining respiration, subnormal level of consciousness, abnormal muscle tone and seizures [42].

Table 2.2 Sarnat clinical staging of hypoxic ischaemic encephalopathy. (Sarnat HB, Sarnat MS. Neonatal encephalopathy following fetal distress, a clinical and electroencephalographic study. Archives of Neurology. 1976; 33:701).

Variable	Level of consciousness		
	Alert/hyperalert	**Lethargy**	**Coma**
	Stage I (HIE I)	**Stage II (HIE II)**	**Stage III (HIE III)**
Muscle tone	Normal	Hypotonia	Flaccidity
Seizures	Absent	Focal or multifocal	Decerebration/ generalized
Complex reflexes:			
Suck	Active	Weak	Absent
Moro	Exaggerated	Incomplete	Absent
Grasp	Normal/exaggerated	Weak	Absent
Tonic Neck	Slight	Strong	Absent
Autonomic functions:			
Pupils	Mydriasis	Miosis	Variable, often unequal poor light reflex, fixed dilated
Heart rate	Tachycardia	Bradycardia	Variable
Level of consciousness	Hyperalert	Lethargic or obtunded	Stupor or coma
Activity	Normal	Decreased	Absent
Neuromuscular control:			
Muscle tone	Normal	Mild hypotonia	Flaccid
Posture	Mild distal flexion	Strong distal flexion	Intermittent decerebration
Stretch reflexes	Overactive	Overactive	Decreased or absent

This staging allows for prediction of neurodevelopmental outcomes and for appropriate clinical management. In order for the prognostic value of the stages to be most beneficial, the examination needs to be of the most severe signs and this must be conducted between one hour to seven days after birth[3].

The Sarnat staging takes other medical symptoms into consideration including seizures. The percentage of infants presenting with seizures differs with Sukha (2014) reporting an incidence of 47% in infants with HIE at CHBAH[43]. Kwon et al. (2010) found a rate of between 44% and 57% in the USA for infants that had and had not received induced hypothermia. Simbruner et al. reported percentages below 40% in Europe in 2010[44, 45]. The staging does not consider Neonatal Jaundice (NNJ) which has also been associated with HIE and may affect the outcome of the condition[46]. There is no agreement on whether induced hypothermia reduces the incidence of seizures in infants with HIE with only some studies finding a difference or what effect seizures might have on later disability[45, 47].

Table 2.3 Thompson score[48]. (Thompson CM, Puterman AS, Linley LL, Hann FM, van der Eist CW, Molteno CD, Malan AF. The value of a scoring system for HIE in predicting neurodevelopmental outcome. Acta Paediatric. 1997; 86: 757–61.

Score	0	1	2	3	Final TOTAL
Limb Tone	Normal	Generally hypertonic	Generally hypotonic	Flaccid	
Level of Consciousness	Normal	Hyper-alert or staring	Lethargic/ Obtunded	Comatose/ Stuporose	
Visible Fits	None	Infrequent < 3/day	Frequent > 2/day		
Posture	Normal/ Other	Fisting and/or cycling	Strong distal flexion	Decerebrate	
Moro	Normal	Partial	Absent		
Grasp	Normal	Poor	Absent		
Suck	Normal	Poor	Absent and/or bites		
Respiration	Normal	Hyperventilation	Transient apnoea	Apnoea requiring IPPV	
Fontanel	Normal	Full	Tense		

There is a modified version of this scaled that considers the presence of seizures, can be used in resource-restrained contexts such as those found in South Africa. This was published by Thompson et al. in Cape Town and is now used in many NICU's both locally and internationally (Table 2.3)[48].

This scale is quicker to administer, requires no additional training and no equipment where access to specialists and MRI's is not always available[48].

2.4 Burden of Hypoxic Ischaemic Encephalopathy

Worldwide, HIE has been known as one of the most important causes of mortality and morbidity in neonates[10]. The incidence of neonatal encephalopathy has been estimated at 3.0 per 1000 live births worldwide with the incidence in developed countries being lower at 1.5 per 1000 live births[7]. Within these live births 0.5 to 1 per 1000 infants have moderate or severe HIE[33].

In developing countries such as South Africa, the incidence of HIE is reported to be 4.6 per 1000 live births[8]. This study completed by Horn et al in 2013 found that it is difficult to determine the incidence of HIE in studies completed in South Africa due to the use of different criteria for the diagnosis. He reported that the incidence varies and that the incidence of HIE in their study where birth weight was >2500 g was 3.8 per 1000 live births with that for moderate and severe HIE being 2.7 per 1000 live births. Data published in a clinic-based study in 2007 found an incidence of 9 per 1000 live births and a hospital based study reported an incidence of 8.3 per 1000 live births in 2009[12, 49]. It can be deduced that the incidence has reduced over the year. Pattinson et al (2007) found that HIE is the leading cause of death in South African infants[50].

2.5 Levels of Hypoxic Ischemic Encephalopathy

Hypoxic Ischemic Encephalopathy (HIE) has a significant impact on the mortality and morbidity of a neonate and is associated with long-term neurodevelopmental deficits. It can be a huge social and financial burden due to the severity of the disabilities of these children as well as loss of quality of life for the children and their families[7, 25, 51, 52].

Developmental outcomes after HIE at birth are associated with different levels of function. Neonates with HIE I (mild neonatal encephalopathy) present with no abnormal neurological signs and no adverse outcomes. In HIE II or moderate neonatal encephalopathy, neonates have a 10% chance of death; and of those that survive 30% will have a chance of disability. In HIE III or severe neonatal encephalopathy, infants have a 60% chance of death and many if not all of those who survive present with neurological deficits in the areas of gross and fine motor skills, social and speech development. These infants present with adverse outcomes including intellectual impairment, cerebral palsy, seizure disorders, cortical visual impairment as well as deficits in auditory, language and sensory-motor processing[3, 18, 34, 42, 51, 53-55].

Treatments that can reduce the effects of HIE need to be researched and incorporated into the management of infants with HIE. While it is appreciated that no forms of specialized therapy can completely reverse the damaging process of HIE, it is important to focus intervention efforts on prevention rather than cure[23]. There is a "window of opportunity" which is evident in a neonate after hypoxic ischemia; efforts to reduce the effects of HIE should focus on this phase[32].

Strategies to prevent or treat HIE include N-methyl D-aspartate (NMDA) receptor blockers (i.e. ketamine, magnesium sulphate or dextromethorphan), Xanthine oxidase inhibitors (allopurinol), Nitric oxide synthase (NOS) inhibitors, free radical scavengers (super oxide dismutase lazeroids) or induced hypothermia[32]. The mechanisms of these drugs as a treatment option are the molecules in the medication, which are able to cross the blood-brain barrier. They target specific mechanisms, which are often not inhibited by induced hypothermia. The ideal goal for these medications would be to use them in conjunction with other techniques i.e. induced hypothermia as a synergist in producing a neuroprotective effect[56].

Hypothermia has been used for many decades, reducing the brain temperature to 28^0C to be used for neuroprotection. This neuroprotection is typically useful during cardiac arrest for open-heart and neurosurgical procedures as well as following a head injury, coronary artery bypass surgery and acute stroke. In paediatrics it has been used in the cases of near drowning victims; this was found to be effective after

drowning victims who were hypothermic after periods of up to 40 minutes under cold water, were found to survive without neurological deficits[7, 33]. There have been numerous studies since to show that neuronal injury can be reduced or prevented in infants with HIE by a minimal reduction in body temperature to 33.5^{0}C to 34.0^{0}C during this "window of opportunity[6, 14].

2.6 Assessing the Infant for Hypoxic Ischemic Encephalopathy

One of the key mechanisms of induced hypothermia is the inhibition of intracellular signalling events, which set off the cascade of cell death[7, 9, 14, 32, 55]. In 2006, the AAP recommended that if an institution made the decision to use induced hypothermia as a therapeutic modality, a rigorous protocol must be followed as well as data collected during neurodevelopmental follow ups to evaluate the effectiveness[16].

Six large randomized clinical trials on induced hypothermia for infants with HIE were published up to 2011 by Jacobs (2011), Simbruner (2010), Zhou (2010), Azzopardi (2009), Gluckman (2005) and Shankaran (2005). All of the trials included full term infants with a diagnosis of moderate (HIE II) or severe (HIE III) neonatal encephalopathy. All infants received induced hypothermia before 6 hours of life and all cooled infants for a period of 72 hours. Gluckman et al (2005) and Shankaran et al (2005) found a statistically significant reduction in major disability as well as death during their trials[57, 58]. Jacobs et al (2011) found hypothermia within 6 hours after birth to be safe and effective in near-term and term newborns with hypoxic ischemic encephalopathy (HIE)[6]. In collaboration, these studies found that death or moderate/severe disability occurred in 44% of infants that were in the induced hypothermia group in comparison to 62% in the control group, at 18 months of age[6, 44, 57-60].

Importantly, induced hypothermia is able to decrease an infant's mortality without increasing the chances of disability occurring in the infant. They also found it to be a safe therapeutic intervention with an understanding that there are acute adverse events i.e. thrombocytopenia and sinus bradycardia secondary to induced hypothermia[6, 30, 44, 57-60].

Two modes of cooling have been evaluated; whole body hypothermia and selective head cooling with mild systemic hypothermia. Initially, whole body hypothermia was thought to be harmful to an already compromised neonate. This, along with the fact that a neonate's brain produces 70% of their total body heat, justified selective head cooling. However, through more extensive research, it was found that cooling the head only did not produce the desired effects. A significant deep brain temperature reduction was only achieved when lowering the full body temperature, as deep brain and core body temperatures are alike. It is therefore necessary to reduce systemic temperature to achieve deep brain cooling[6, 33].

All of these studies [30, 44, 57, 58, 60] were performed in developed countries throughout the world, whereas one more specific study by Kali et al. in 2015 done in South Africa found whole-body induced hypothermia as a feasible option[26]. This study was carried out at Tygerberg Children's Hospital in Cape Town, South Africa, which is a tertiary public hospital. The infants who were used for the study were considered full term infants, with a minimum birth weight of 1.8kg and had to meet the criteria for moderate to severe encephalopathy or seizures. The protocol used was to induce whole-body hypothermia for a period of 72 hours to a temperature of 33^0C to 34^0C using a rectal thermometer as a means of measurement. The sample that was evaluated consisted of 100 infants over a three-year period, 32% with mild HIE, 45% moderate HIE and 23% severe HIE (using the Thompson score). Importantly, there was no significant differences found in outcomes of those children who were born inside the hospital versus those outside of the hospital setting, provided that the cooling was performed in the six-hour critical period[26].

In settings where a NICU is not available, induced hypothermia is not considered safe or effective. There are, however, institutions in South Africa with NICUs and although these have limitations i.e. low socioeconomic situations, moderate mortality rates as well as difficulty with following up these children, these NICUs are effective. This is available more often at tertiary institutions but not always at primary and secondary institutions. These studies highlight that whole-body hypothermia is a feasible option in a resource-limited setting (i.e. CHBAH) provided that a similar protocol is followed to those clinical trials discussed above[26, 27, 30]

Whole-body hypothermia is achieved by turning off the transport incubator and exposing the neonate to the ambient temperature. Specialised 'gel packs' are applied across the neonate's chest and/or under the head and shoulders[6, 15, 16]. The neonate is closely monitored and supported by a nursing sister as well as neonatologist. Kali et al. emphasised the importance of monitoring and support, as there are adverse effects i.e. changes in blood pressure and heart rate, to inducing hypothermia in infants[26]. During the maintenance period gel packs are applied when the temperature rises above 34^0C. After 72 hours neonates are rewarmed over eight to 12 hours by half a degree every two hours, this is closely monitored. Neonates are monitored for oxygen saturation, respiration rate, continuous core temperature, heart rate, arterial blood pressure and urine output. Certain other parameters are measured such as liver function; coagulation profile; blood gases; complete blood cell count including platelets; lactate, glucose, electrolyte, urea and creatinine levels; and calcium and magnesium levels[6, 15, 16]. It is vital for the transport, referring and treating teams working with these infants to be well trained to ensure correct assessment for early recognition and adequate management in order for these infants to benefit from whole-body hypothermia[56].

2.7 Limitations and controversies in the use of Hypothermia in Hypoxic Ischemic Encephalopathy

What is particularly challenging for a neonatologist is identification of infants with birth asphyxia who are at risk of future disability and which ones may benefit from induced hypothermia. This is because it is difficult to distinguish between the factors resulting in hypoxia, and whether or not it is related to encephalopathy, antepartum factors or underlying congenital abnormalities[6, 33]. Other challenges include the time taken to transport the infant to an appropriate facility, the narrow "window of opportunity", irregular and inconsistent implementation protocols and the equipment for the correct monitoring of these infants during induced hypothermia[56]. Controversial issues include, the level of hypothermia required, how soon after the insult or birth does cooling need to begin and the duration and the method of cooling. There is also a risk of arrhythmia, coagulopathy, renal failure, hypotension, and infection amongst others[6, 33].

Wintermark found induced hypothermia to be a helpful strategy in preventing brain injury in some infants with birth asphyxia but not for all of them. There are multiple interests in understanding the extent of brain injury to either refine neuro protective strategies or add to the neurorestorative strategies already used. There are potential alternatives to induced hypothermia; however, none have proven as effective as induced hypothermia as yet. Further and more extensive research is required[56]. In spite of the controversies, the majority of researchers agreed that induced hypothermia reduced mortality without increasing neurological deficits and that it decreases long-term neurodevelopmental disability[6, 14, 15, 53, 59].

In spite of this, induced hypothermia is a possibility even with limited resources as there are cost effective feasible options exist with gel packs, water bottles, passive/accidental cooling as well as servo controlled cooling fans. However, more studies need to be done on the efficacy of this. In a personal communication by Nakwa, that describes a study that was done on 98 infants that received induced hypothermia at CHBAH, 83% presented with HIE II and 15% presented with HIE III. Griffiths scores at 12-18 months for these participants were 25% for <85, 60% at 85-100 and 15% > 100. The Griffiths scales developed in 1960 were designed to determine development in children from 3 to 18 months, these scales are compiled and the extent of delay is determined. A score of < 85 is considered a low average, 85 – 100 is considered average and >100 is above average. This study further emphasises that limited resources make these infants difficult to manage according to protocol and that long term management is essential[61]

The criteria used to consider an infant for induced hypothermia at CHBAH are presented in Table 2.4[14, 30, 44, 58, 59, 62]..

Table 2.4 The criteria for induced hypothermia at Chris Hani Baragwanath Academic Hospital:

Infants born at ≥ 34 weeks
Infants weighing ≥ 2000g
Infants that have a continued need for resuscitation or
An Apgar score ≤ 5 at 10 minutes or
Infants presenting with metabolic acidosis (pH < 7.00 or base deficit ≥ 16 mmol/L based on arterial blood gas within 60 minutes of life)
Thompson score ≥ 7 and
Encephalopathy present based on the Sarnat staging of HIE.

2.8 Neurodevelopmental Disability as a result of Hypoxic Ischemic Encephalopathy

Research shows that infants who survive HIE are at higher risk of developmental deficits. They often present with multiple deficits, they can have sensorineural hearing loss, visual loss (CVI), feeding difficulties, gross and fine motor deficits, sensory modulation disorders, maladaptive behaviour, as well as cognitive disorders. Using integrated augmented EEG (aEEG) and clinical evaluation, the severity of HIE can be determined. Infants with HIE II showed less risk of death or severe disability than those with HIE III[62].

Children with tonal changes i.e. hypotonia or any form of abnormality on cranial sonar should be followed up regularly until there are no longer concerns. Those infants diagnosed with HIE II and HIE III who present with feeding difficulties would benefit from referral to a speech therapist and in severe cases to a dysphagia clinic or feeding team. It is vital to refer the infants earlier rather than later as these parents require support[4]. An acute intrapartum hypoxic event resulting in cerebral palsy needs to be long enough to result in this diagnosis. It is evident that hypoxic ischemic encephalopathy plays a role in the contribution of the aetiology of cerebral palsy[63].

South African studies conducted at Charlotte Maxeke and Tygerberg hospitals found that the majority of infants had no or minor impairments. Impairments can include developmental delay, speech delay as well as features of autism[7, 26, 54]. Should an infant survive HIE, deficits in the hippocampus and striatum can result in higher risk of memory, behavioural and cognitive problems[7, 54]. When the infants have survived, resultant conditions such as profound intellectual impairment and cerebral palsy are easily recognizable but disabilities such as mild intellectual impairment, subtle learning disabilities and language impairment may go unrecognized[7].

In the Total Body Hypothermia for Neonatal Encephalopathy (TOBY) study in the USA, it was found that about a third of the children who received induced hypothermia presented with moderate to severe disability. A similar percentage of children who did not receive induced hypothermia also had moderate to severe disability[64]. Simbruner et al. (2010) found a much higher incidence (60%) of moderate and severe disability in their sample of children who did not receive induced hypothermia in a study conducted in Europe. The percentage of disability (moderate and severe) in their induced hypothermia group was approximately 20%[44]. All these studies reported that induced hypothermia did not result in an increased proportion of survivors with severe disability[44, 58, 65] and confirms a reduction in severity of disability and mortality rates with induced hypothermia[57-59, 66].

These deficits can still be associated with in-grade retention, poorer health status, higher rates of school failure and special education placement. Those identified as non-disabled survivors of moderate neonatal encephalopathy were found to have adequate perceptual motor skills as well as receptive vocabulary, however, it was evident that these children had delays in spelling, reading and arithmetic and they were typically one grade behind other children at school. It was also found that these children did not have cognitive fallout but did have sensorimotor, language, narrative memory and sentence repetition difficulties[67].

It is therefore important to assess cognitive capacity, behavioural and educational development as well as motor impairment as these skills are important to functioning in daily life and may have a profound impact on self confidence, school achievements

and ability to cope with life in general[19]. It is therefore recommended that infants with perinatal asphyxia be assessed using a standardized measure to ensure all areas of development are evaluated[4].

2.8.1 Assessment of Neurodevelopmental Disability

The extent to the effects of hypothermia can only truly be understood if these infants are followed up and evaluated into their childhood. Evaluation of the long term effects of perinatal asphyxia are thought to be most effective at an age for which most standardized screening tools have been developed for, namely 18 months and older[18]. However, many babies have early indicators of disabilities, therefore an examination of children as early as 6 weeks after birth may provide insight to the magnitude of the problem. The Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III), is a standardized test that examines all areas of a child's development from one month until 42 months[5].

2.8.2 The Bayley Scales of infant and Toddler development

The Bayley Scales of Infant and Toddler Development – Third Edition (Bayley- III) was designed with the purpose of identifying children who are presenting with developmental delay. The information gathered in the test also assists with intervention planning. The test assesses development between the ages of one to 42 months, and takes from 30 to 90 minutes to administer, dependent on the age of the child. The test is norm-referenced and was created to assist health professionals to identify issues early and to address early childhood deficits before they become lifelong problems[5].

Bayley-III is a unique assessment that emphasizes that development does not follow a well-ordered pattern of abilities but rather fluctuates in an individual child over time. There are specific directions in the administration, sequence and speed of administration which are based on a number of factors such as the child's success rate, age and temperament[5].

In the assessment there are three scales:

- Language scale:
    - Expressive communication

    - Receptive communication
- Cognitive scale
- Motor scale:
    - Gross motor
    - Fine motor

There is also an adaptive behaviour questionnaire and a social-emotional scale, which is usually completed by the parent or caregiver. In order to understand the assessment scales, it is important to understand each scale in depth and how these develop[5].

Bayley-III was found to have strong internal consistency. Moderate to high correlation scores for concurrent validity with tests such as PDMS–2 (r=0.55– 0.59), ABAS–II (r = 0.58–0.70) and Bayley–III (r = 0.50–0.60) in areas that measure similar domains. Its weakness is that normative information is based on the US population for infants one month to 42 months, however this test can be used to compare a child to themselves and normative information does not have to be used.

Johnson et al compared the Bayley Scale of Infant Development, Second Edition (BSID-II) with Bayley–III to determine a consensus on the classifications of neurodevelopmental delay. It was demonstrated that the cognitive and language components of the Bayley – III underestimated the delay in these children by at least 1.1%. It is important as very small children presenting with developmental deficits may be missed by the Bayley-III due to this underestimation and subsequently may not be referred for therapeutic intervention[68].

Research[69, 70] shows a trend for younger infants to have higher scores on the Bayley-III particularly below 10-12 months overall. This has been attributed to the difficulty in providing sensitive items when assessing younger infants. This presents a possible weakness in the Bayley-III when using the measure in longitudinal research over time in the assessment of infants. The cut offs on the Bayley-III should therefore be considered with caution when predicting developmental outcomes in children, although the test is used extensively in research and is considered a gold standard[68].

The Griffiths Mental Development Scales – Extended Revision (GMDS–ER) is another widely used measure used to determine the rate of development of young children. It

includes six sub-scales including locomotor, personal-social, language, eye and hand co-ordination, performance and practical reasoning[71]. It has been used to assess both specific as well as general features of development. Studies have been conducted on children between the ages of two and eight years in South Africa using this test but not a lot done with infants[72].

In a study done by Beail, results found that the GMDS–ER was not interchangeable with the BSID-II in spite of high correlations in the scores, as it was also evident that scores on the GMDS were higher. They suggested that the BSID-II was in fact the preferred test. The GMDS–ER presented with higher age equivalents than the Bayley-III and it requires specialized training courses accredited by the Association for Research in Infant and Child Development (ARICO) whereas the Bayley-III training can be done via on-site workshops or an administration DVD[73, 74]. The Bayley-III was developed in the United States of America (USA) but a study done in South Africa in 2013 found that it is a suitable tool for populations of black urban Africans in Gauteng, South Africa. They found some differences in the norms with higher language and motor scores on the Bayley-III for the South African infants compared to the USA norms[70]. Consequently, the Bayely-III was chosen as an assessment tool for this research study.

2.9 Development in Infants

South Africa is a country that has and is facing multiple challenges. These challenges can potentially have an adverse effect on the development of infants. The challenges include but are not limited to Human Immunodeficiency Virus (HIV), unemployment, tuberculosis, poverty and disease. Development is a complex process that is influenced by numerous factors and is complicated because there are variations in the various ages or age bands where milestones are acquired. Development is affected by social and physical circumstances i.e. nutrition, poverty, quality of stimulation, geographical location, HIE and exposure to toxins and violence, etc. as well as individual characteristics i.e. gender, genetic make-up or personality[70].

In order to understand development, a more in-depth understanding of the components of development is necessary.

2.9.1 Language Development

Auditory processing is a necessity for both receptive and expressive language. It plays a vital role in a child's awareness of their environment particularly social awareness. Auditory information is integrated with the other sensations of proprioception and tactile input in and around the mouth as the child vocalizes. With time, the child begins to experiment with creating various sounds that they have heard their parent or caregiver make. As the child vocalizes, their parent or caregiver will attach meaning to these vocalizations and this helps the child to attach meaning to these sounds. By their first birthday most children will have a small vocabulary of words that they use meaningfully to communicate their needs and desires to their parents and caregivers[67]. There are no specific studies that have been done on language development in HIE, however, an association between language and cognitive development was made by Carson et al. in 1998[75].

2.9.2 Cognitive Development

Cognition is a process of acquiring knowledge and includes the ability to represent events, objects and relationships in their minds as well as conceive, recognize, sense, perceive, reason and imagine[76]. A child will use all of their experiences to integrate new knowledge into already laid structures and to adapt existing structures to familiarize new information. During the first six months of life, a child will learn more about their body and the effect that their actions have on their environment. A child will focus their interests on the actions of objects and sensory feedback that is provided by the actions. They will primarily use sensory feedback through smell, taste, vision, hearing, vision and movement[67].

Repetition of actions is important for learning, as well as play, focused on the actions that can be performed with an object, i.e. banging, mouthing and shaking. The infant becomes more goal-directed with time and begins to use play tools to advance their understanding of the function of objects. Cognition is believed to develop from concrete to abstract, simple to complex and from personal to worldly concerns. In childhood, appropriate development is vital as it leads to cognitive maturity into adulthood, which will culminate into goals, values and plans[20, 77, 17, 38].

2.9.3 Motor Skills Development – Gross Motor

A child begins moving prenatally in response to tactile and vestibular input that is experienced inside the womb. An infant will show an impressive amount of development during their first vital year of life, this development is a complex and dynamic process. This first year is characterized by variation and exploration. The most important skills for a child to develop are sitting, walking, crawling, standing, reaching and grasping. All of these motor responses contribute to the development of perceptual organization and development. The expansion of all these skills helps a child to explore their environment[20, 78, 79].

2.9.4 Motor Skills Development – Fine Motor

Fine motor skills begin to develop through a child's exploration of their environment. With the acquisition of gross motor skills a child will develop their fine motor abilities. A child's perceptual skill development is reinforced by a child's improved manipulation skills; in turn, this enforces perceptual development[20].

2.9.5 Adaptive Behaviour

This section of the Bayley-III was developed to evaluate the parent/caregivers understanding of an infant/child's functional abilities in components of development of communication, community use, health and safety, leisure, self-care, self-direction, functional pre-academics, home living, social and motor. It facilitates a more comprehensive understanding of development as it includes the caregivers impression of their child[80]. There is limited literature available on this component of development.

2.9.6 Socio-Emotional Development

There is a dramatic emotional transition that is experienced by an infant when they move from their comfortable, warm and protective womb space to the moment of birth. Initially a neonate's system's focus is on the maintenance of body functions i.e. their gastrointestinal, cardiovascular and respiratory systems. With the maturation of the infant's system the focus will shift from survival to increasing competence in their interactions with their environments. Trust and mistrust is a prominent theme in their emotional development at this stage and this is reliant on the infant's

relationship with their caregiver. Bonding develops from share experiences with a caregiver over time. This is evident in the advancement of physical contact between the caregiver and infant, hence the importance of face-to-face engagement of a parent with their infants as part of the development of attachment. As their confidence improves a child will begin to engage with others[20]. There is limited literature available on the social-emotional components of development.

2.9.7 Developmental delay in infants and children with Hypoxic Ischaemic Encephalopathy

A study by Sukha (2014) on the motor outcomes of infants, with HIE II and HIE III between the ages of 12-14 months, it was found that the amount of disability is highly variable, however HIE III children were found to have more severe disabilities. It was also evident that fine motor skills were slightly lower than the outcomes of gross motor skills particularly those infants who were diagnosed with HIE II[43].

Chalak et al (2007), when assessing children with HIE used the Bayley-III in the USA. They found 50% of the children presented with normal development in cognitive, language and motor components, while 37% were at risk of developmental delay and 13% presented with moderate and severe developmental delay[81].

It has also been found, through previous studies, that the infants with birth asphyxia showed evidence of intellectual deficits. These factors were taken into consideration when analyzing the data for this study[4].

2.10 Treatment of Neurodevelopmental Disability

Research on deficits that occur in infants with HIE (even after whole-body hypothermia) indicate that early childhood intervention is critical in order to improve these impairments[18].

2.10.1 Early Childhood Intervention

Early intervention refers to intervention during a child's most critical period of development, that being between birth and three years of age[20]. During these first three years a child learns to adapt to a new sensory world outside of the womb. They have to adapt to touch and proprioception, learn how to perceive their environment

in an appropriate manner, adapt to movement as well as gravity. Children develop in four major developmental areas, being gross motor, fine motor, language, social and emotional development. These do not develop individually but rather as an overlap of different skills and different components of the same skills at the same time. This occurs in spurts due to the fact that the brain has to have time to consolidate skills, as they are acquired[29].

There has been an improvement in predictive data due to the increasing development of statistical and epidemiological methods as well as improved understanding of the pathophysiology of perinatal asphyxia. As a result prognosis can be used as a tool for understanding the necessity of follow up as well as the frequency and type of follow up required[4].

The goal of early intervention is to reduce or avoid limitations in cognitive, physical and emotional development and to reduce the effects that environmental and biological risk factors have on infants[20]. Regardless of which team member provides the primary service, the goal must remain the same – functional independence within a child's typical daily tasks[21].

2.10.2 Role of the Transdisciplinary Team

Occupational therapists, physiotherapists and speech therapists design their intervention programmes based on the assessment and identification of infants with delays or disabilities[22]. Occupational therapists work holistically with the child and the family to promote a child's sense of self-worth, mastery, independence and their confidence in emotional, psychosocial and physical development. Occupational therapists treat children in their everyday occupations and activities, which allow the children to experience normal movement in several different ways. The services that are provided are intended to assist families as well as caregivers to improve a child's occupational performance within different environments[82].

Occupational therapists with special interests in paediatrics help children with special needs to overcome their limitations. The goal is to promote personal growth, development, independence and to improve quality of life. Approaches are generally holistic, client and family centred. It is important for occupational therapists to

examine evidence and draw on a range of theoretical models in order to use best practice standards[83].

The developmental skills intervention approach is often used in early intervention programmes and focuses on the learning and mastering of typically sequenced milestones. The intervention will be targeted on identifying skills at the next higher level. In this approach children will be encouraged to engage in play-based activities, which will target specific skills. The therapist provides parent guidance to encourage practice at home for reinforcement of therapy[82].

Therapists have all too often ignored the specific and personal dimensions that are involved in parenting and rather view this as a common experience. There has been a recent shift in focus in occupational therapy towards a family-centred approach. Central to this is the involvement of parents as well as other family members as part of the team that plans and provides interventions. Involving families in this manner may result in meaningful outcomes for therapy. However, this approach can pose challenges as it requires a shift in thinking from the traditional child focused approach. It is vital that occupational therapists develop their skills in this area and collaborate with parents towards a more family-centred approach[82, 84].

Occupational therapy based on the neurodevelopmental therapy (NDT)/Bobath concept is used to improve motor ability and sensation, perception and quality of hand eye function, which are all necessary in functional activities. Neurodevelopmental treatment (NDT)/Bobath is an interdisciplinary clinical practice model that endorses that everyone concerned with a child's management work closely together and have the same intervention goals. The NDT/Bobath model highlights the effectiveness of a combined approach from all rehabilitation professionals rather than each therapist working in isolation when treating the child[85, 86].

The physiotherapists role is predominantly focused on mobility/motor abilities, joint abnormalities in the lower limbs and spine, as well as the facilitation of postural control and more normal movement patterns with good biomechanical alignment. Along with the occupational therapist the physiotherapist will assist with more appropriate positioning at home as well prescribing and monitoring seating devices.

The speech language therapist and audiologist's role is focused on the evaluation, treatment and monitoring of eating and drinking, hearing as well as speech and language development[85, 86].

2.10.3 The Neurodevelopmental Treatment / Bobath Concept

The rehabilitation aims for children with neurological impairment, are to guide them towards their greatest potential and assist them to ultimately achieve as much independence as they can. Bobath and Bobath developed the concept of NDT[85-87].

Bobath quoted by Graham et al stated:

"the Bobath Concept is far-reaching and open, it enables us to go on learning and to follow continuous scientific development. Neurodevelopmental treatment/Bobath is a holistic approach dealing with the quality of patterns of coordination and not only with the problems of individual muscle function. It involves the whole person, not only his sensory-motor problems but also problems of development, perceptual-cognitive impairment, emotional, social and functional problems of the daily life as well." p. 58 [86].

Neurodevelopmental treatment/Bobath provides the occupational therapist with the opportunity to work in and play a vital role in the transdisciplinary team as well as to engage in parent guidance and education throughout the therapy process. Early NDT/Bobath should begin between the ages of two to three months. The reason for that is that antigravity voluntary movements have not yet emerged and that abnormal movement patterns have not yet been established. With early intervention we have the opportunity of integrating normal sensory-motor experiences before habitual abnormal movement patterns set in[22, 86].

As effective as the NDT/Bobath concept is for neuro rehabilitation, it does not provide a complete platform and it should not be used in isolation but rather with other adjuncts and approaches[87]. According to the Neuronal Group Selection Theory (NGST) and the social model, a child's environment is of utmost importance and has a significant impact on their development. It is vital to understand this and work with their families towards a quality of life for children with disabilities[82, 83].

2.11 Summary

It is evident worldwide that 10% to 60% of affected infants die from HIE and that 25% of survivors have long-term neurodevelopmental outcomes[7]. If high-risk infants are provided with the correct treatment including induced hypothermia within six hours of birth, if neurological deficits are identified and treated in these children early, they can be assisted to reach their potential and develop their abilities in the most normal way. In a study done in South Africa by Joolay Y et al (2012), 288 South African paediatricians and neonatologists (76%) were of the opinion that therapeutic hypothermia is an effective treatment method in the reduction of neurological deficits in infants with HIE[88].

With early therapy it is possible to integrate normal sensory-motor experiences before the child is able to establish a habit of abnormal movement patterns. Without help these children may only develop abnormally. If rehabilitation is delayed they may have established abnormal patterns of posture and movement or maladaptive behaviour limiting the effectiveness of the intervention efforts.

CHAPTER 3: RESEARCH METHODOLOGY

3.1 Research Design

An experimental quantitative method of research was used in this study as the group who had received induced whole-body hypothermia and those who have not were evaluated to determine the interaction with the dependent variables of developmental outcomes (motor, cognitive, language, socio-emotional and adaptive behavior) between these two groups. A pre-test and post-test design with these two groups was used. A pre-test was done at the initial assessment when infants were between the ages of five to 16 months. The groups were both reassessed after three to nine months in conjunction with their follow ups with the paediatricians as well as their transdisciplinary follow up appointments which constituted the post test asessments. Infants with hypoxic ischemic encephalopathy, referred or screened from the HIE or Neonatal Follow Up Clinics (NNFUC), all received early trans disciplinary monitoring and intervention with the focus on neurodevelopmental therapy (NDT).

3.2 Study Sample

3.2.1 Study Population and setting

The study population consisted of infants between the ages of five months and 24 months who were diagnosed with HIE regardless of their family's culture, level of education and socioeconomic status. The HIE clinic at CHBAH is a clinic involving neonatologists, a speech therapist, physiotherapist and occupational therapist. Its purpose is to identify neurodevelopmental delay in infants with HIE and to manage these medically as well as from a therapeutic perspective. It is vital for case management of children who are often presenting with complex multidimensional deficits.

3.2.2 Sample description of participants

The possible participants were identified on screening of infants who were booked for the HIE clinic. Whilst the infants were waiting for the neonatologists, a colleague

(speech therapist or a physiotherapist) screened the infant's files to identify the infants appropriate for the study.

All infants who were assessed were being managed at the HIE clinic and referred for assessment, therapy and monitoring to the transdisciplinary team which included a physiotherapist, speech therapist and occupational therapist.

3.2.2.1 Sample Selection

The participants were selected according to the following criteria:

Inclusion criteria:

Infants selected should:

- be diagnosed with HIE II and HIE III by the neonatologists at CHBAH according to the diagnostic criteria (see Appendix A),
- be born full term at 34 – 40 weeks or term appropriate gestational age (TAGA),
- have a birth weight above two kilograms (kg).

Exclusion criteria

Infants selected should not:

- require home oxygen,
- have an additional neurological, chromosomal, genetic, congenital or other disorder, which may cause developmental delay.

3.2.3 Sample Size

The sample of infants were recruited from the HIE clinic at Chris Hani Baragwanath Academic Hospital (CHBAH). A sample size of 43 infants were assessed, these were all the infants that attended the HIE clinic diagnosed with HIE II and HIE III during the study period. The sample size for the reassessment was 31 infants, these were the infants that returned for their follow appointments with the transdisciplinary team and/or the paediatricians at the HIE clinic. In the total sample size that was assessed only four were diagnosed with HIE III whereas 39 were diagnosed with HIE II. All of the infants with HIE III returned for reassessment whereas 27 infants with HIE II were reassessed. This is in contrast to the initially proposed sample of 31 infants per group in the research protocol. This size was based on a 5% significance level at 80%

power. This was based on the average difference between the groups who had hypothermia and those who did not in a study by Akar et al[89] where both groups achieved a change of 0.3 points (SD 4.2) on the Bayley Scales of Infant and Toddler Development – 3rd Edition (Bayley-III) after at least three to nine months of intervention.

3.3 Measurement Techniques

3.3.1 Demographic Questionnaire (Appendix B)

The demographic form that was developed for this research study was a combination of forms including typical information obtained for infants undergoing developmental assessments as well as those children who are assessed at the paediatric neurological rehabilitation clinic. The demographic history included birth history, medical history including length of stay in the maternity ward, as well as co-morbidities. An attendance register was kept with all the essential information as well as identifying information that was kept separately by the researcher. This included age, address, contact number and whether or not the infant received induced whole body hypothermia at birth. The attendance register was used as a manner of tracking children's attendance as well as ensuring that all or most of the children had follow up dates with their doctors.

Once the children were screened to determine their suitability for participation in the study, verbal and written consents were obtained from the parents. The parents were then asked all of the questions on the demographic questionnaire, to avoid any confusion. All information from the demographic questionnaires were compiled and kept on a confidential database that was kept in a secure location throughout the research study.

3.3.2 Bayley Scales of Infant and Toddler Development – Third Edition (Bayley – III) (Appendix C)

The Bayley Scale of Infant and Toddler Development (Bayley-III) was designed to identify developmental delay in young children and to provide information on intervention planning. It is a measure of a child's socio-emotional, cognitive, language, motor and adaptive behaviour development. The therapist observed components of

development are cognitive, receptive language, expressive language, fine and gross motor. The parent/caregiver-evaluated components of development are social-emotional and adaptive behaviour[5]. Modification was necessary in the form of translation of the parent/caregiver-evaluated components as well as explanation of concepts not understood by parents.

The average reliability coefficients for the five subtests ranged from 0.94 to 0.98. Test-retest reliability (r = 0.67–0.94) and average stability coefficients were 0.80 or greater across all ages. All inter subtest correlations are statistically significant and correlations between the scales were in the low to moderate range.

3.3.2.1 Scoring of the Bayley–III

Each component of the Bayley-III (cognition, gross and fine motor, receptive and expressive language, socio-emotional and adaptive behaviour) was scored and a raw score was produced. This score was recorded on the front of each participants assessment form. At a later stage these raw scores were converted into scaled scores, composite scores, percentiles and developmental ages.

3.4 Research Procedure

Initially, permission was obtained from the Human Research Ethics Committee at the University of the Witwatersrand – Clearance certificate number M140489 (Appendix D). Once ethics permission was obtained, permission was obtained from the CEO/management of Chris Hani Baragwanath Academic Hospital (Appendix E) prior to seeking permission from individual departments. Permission was then obtained from the occupational therapy (Appendix F) and neonatology (Appendix G) departments through the heads of departments. All permission letters included a description of the purpose of the study, the objectives of the study and a basic procedure.

All infants with birth asphyxia are admitted to the NICU at Chris Hani Baragwanath Academic hospital. If the infant is a candidate to receive whole-body induced hypothermia (in accordance with the selection criteria) they will remain in the NICU until the hypothermia is complete and once they are medically stable they will be transferred on to the maternity ward. The infants that do not receive whole-body

induced hypothermia will remain in the NICU until medically stable. These infants are booked for the HIE clinic as outpatients on discharge, they are followed up seven to ten days after discharge.

The researcher attended the HIE clinic on a weekly basis. Infants are booked for appointments at the HIE clinic if they are considered high-risk after birth asphyxia. The neonatologists at CHBAH determine this. This clinic is responsible for determining developmental delays or concerns in these infants and for advising parents/caregivers on the management of these as well as monitoring these concerns. Children are followed up every three months by the neonatologists, if they are minimally involved. If the doctors are more concerned they will follow these children up in four-week intervals. The transdisciplinary team (physiotherapist, speech therapist and occupational therapist) will assess these infants/children in conjunction with their neonatology appointment.

The infants that were brought to the neonatology follow up appointments were screened by the transdisciplinary team while sitting in the waiting area. A speech therapist or physiotherapist working at the clinic with the researcher would read through the patients file to check if the infants fit the inclusion criteria, were diagnosed with HIE II or HIE III and whether or not they had received whole-body induced hypothermia. This information was kept hidden from the researcher and only information on birth history was provided to the researcher.

Initially the parent's participation in the study was verbally requested and once this was given written consent was requested (Appendix H). The parents were provided with an information sheet on the purpose of the study as well as the logistics and requirements of the study (Appendix I).

The study was conducted for a year from June 2014 until June 2015 in an attempt to achieve the sample size required for the study. Unfortunately due to several variables a smaller sample size than was proposed was adopted. These variables included staff shortages i.e. when staff were on leave, parents/caregivers resource limitations and time constraints.

The parents of the infants were informed that the infant would be assessed and that they should continue with the programme provided by the transdisciplinary team

with their regular appointments. The infant would be reassessed after three to nine months. This reassessment period was in conjunction with the infant's neonatologist and transdisciplinary follow up session, parents/caregivers were provided with transport money in order to return for reassessment. Reassessment was delayed due to parents/caregivers having difficulty bringing their child to the hospital for various reasons i.e. multiple infants at home and not having assistance for care of these infants. In spite of there being a great variability in the time frames the expectations on the assessment tool for the infants also increases as they become older consequently the influence of time is minimal. Numerous attempts were made to contact the parents/caregivers of infants that did not return for reassessment. A list of the defaulters were also provided to the nurse at the HIE clinic as well as the transdisciplinary team to ensure that should the infant return and the researcher be not aware of this that the researcher be contacted to inform her of this.

3.4.1 Data Collection

The background questionnaire was used to record a full and comprehensive demographic history from the parents/caregivers.

The information regarding whether the infant received induced hypothermia or not, was not disclosed to the researcher. The transdisciplinary team members and nursing sisters, working with the researcher, recorded this information on the attendance register and a separate information sheet to ensure this non-disclosure. The infants were assessed by the researcher using the Bayley-III. This was done at the HIE clinic on the same day as the infants were recruited for the study; which was convenient for the parents/caregivers. The assessment took between 30 to 60 minutes, dependent on the age of the infant.

The raw scores were recorded for each component of the Bayley-III on the Bayley-III score sheet and these were converted into scaled scores, composite scores, percentiles and developmental ages. This data was provided to the neonatologists and transdisciplinary team.

All participants attending the HIE clinic were assessed by the neonatologist and a member of the transdisciplinary team (occupational therapist, speech therapist or physiotherapist). The transdisciplinary team's assessment is based on the Bayley-III

in a more basic tick off form, the infant/child will be assessed according to cognition, receptive and expressive language, gross and fine motor skills. As this is a transdisciplinary approach either an occupational therapist, speech therapist of physiotherapist will assess the child, not all of these children received all three disciplines. The intervention program includes an education as well as demonstration (with the child) of basic skills i.e. facilitation of prone play dependent on the area of concern highlighted in the assessment. The therapists will also highlight the importance of play and how to facilitate this within parent/caregivers constraints.

3.5 Ethical Considerations

Ethical clearance was obtained from the Human Research Ethics Committee at the University of Witwatersrand (Appendix D). Permission was obtained from the CEO, Head of the Neonatology unit, Ethics Committee and Occupational Therapy department at Chris Hani Baragwanath Academic Hospital (Appendix E, F and G) to carry out the study.

The caregivers of the infants were provided with an information sheet on the purpose of the study and how their infants' participation will benefit the research (Appendix I). An informed consent form to complement this information sheet was signed by the parent to give written consent for the infant's participation in the study (Appendix H). The parents/caregivers were informed that if they were not willing to allow their infant to participate that there would be no consequences in terms of their therapy or medical care. Parents/caregivers were informed that the study was voluntary and that they could withdraw their infants from the study, also without consequence.

All identifying data about the infants were kept separate in a secure place by the researcher and no names were used on the data collection sheets thus ensuring confidentiality through the use of codes and not names throughout the study.

Caregivers were informed that they would be able to request feedback from the research. The participants did not incur any costs through participating in the study. The analysed transdisciplinary therapeutic service was the typical service that the

children would be receiving, irrespective of whether they participated in the study or not.

3.6 Data Analysis

All data was captured in Excel spread sheets. All scores for the Bayley-III adaptive behaviour, socio-emotional, cognitive, receptive language, expressive language, fine motor and gross motor development were captured and divided according to the groups indicating if the infants received induced hypothermia or not, and whether they were diagnosed with HIE II or HIE III.

Demographic and medical data were analysed using descriptive statistics using frequencies. The data were analysed according to whether the infants received induced hypothermia or not and the groups were compared to determine if they were comparable for demographic and medical f variables using Fischer's exact tests.

Scores on the Bayley–III for baseline assessment and reassessment were presented as scaled scores and were analysed using a median and quartile ranges for descriptive statistics, as the data were not normally distributed.

Non-parametric statistics were used because of the small sample size and a Mann Whitney U test was used to determine significant differences between the developmental outcomes of the group of infants who received induced hypothermia versus those who had not at both baseline assessment and on reassessment. Effect sizes were calculated to understand the magnitude of the treatment effect from one experiment to another, irrespective of the sample size, and to quantify the size of the differences between the groups[90].

The mean developmental score for each of the subtests on the Bayley-III were compared for baseline and reassessment for both the group who received and the group that did not receive induced hypothermia. A frequency of the scaled scores was analysed for each of the subtests in order to determine the percentage of infants who had typical scores or above, as well as those with mild, moderate or severe dysfunction.

A Wilcoxon's sign rank test was used to compare within group changes from baseline assessment and reassessment results of the participants in each group for those who did and did not received induced hypothermia.

The difference in development between infants with HIE II and HIE III was also analysed to determine the difference but the small sample of participants with HIE III meant that Fisher's exact test had to be used.

CHAPTER 4: RESULTS

4.1 Introduction

This chapter presents the results of this study including the demographics of the infant participants, medical history and family demographics. It continues with the results of the Bayley Scales of Infant and Toddler Development (Bayley–III) looking at the developmental outcomes of these infants.

The total number of infant participants recruited into the study was 43 presenting with HIE (type II and III) between the ages of five and 16 months. The total number of infants who received whole-body induced hypothermia was 29 (67%). Within the total number of participants, four presented with HIE III and 39 with HIE II.

Twenty eight percent (28%) of the participants were lost to follow up. Of these, all 12 were in the HIE II group, four of whom had received induced hypothermia while eight had not.

A total of 31 participants were reassessed after a period in the transdisciplinary therapy programme. This period differed depending on when the infants and toddlers were recruited into the study from the Hypoxic Ischemic Encephalopathy (HIE) clinic at Chris Hani Baragwanath Academic Hospital (CHBAH).

4.2 Demographics

4.2.1 Demographics of Participants

4.2.1.1 Age and Gender

The ages of the participants at baseline assessment ranged in age from five to 16 months with the majority being between five to six months of age (32.56%) (Table 4.1). There was no significant difference in the ages of the participants who did and did not receive induced hypothermia, however, those who received induced hypothermia had a greater range in ages from five to 16 months. More than three quarters of the group who did not receive induced hypothermia were male with very few being female. Again in terms of gender, the groups were not significantly different (Table 4.1).

Table 4.1 Age and Gender of the infant participants (n=43)

		Total sample (n=43)	Induced hypothermia n=29	No Induced hypothermia n =14	p value
		Percentage (n = 43)			
Age (months)	5 to 6	32.56% (14)	37.92% (11)	21.43% (3)	0.56
	7 to 8	30.23% (13)	24.12% (7)	42.86% (6)	
	9 to 10	13.96% (6)	10.43% (3)	21.43% (3)	
	11 to 12	13.96% (6)	17.22% (5)	7.14% (1)	
	13	6.98% (3)	6.88% (2)	7.14% (1)	
	16	2.33% (1)	3.43% (1)		
Gender	Male	72.1% (31)	65.52% (19)	85.72% (12)	0.16
	Female	27.91% (12)	34.48% (10)	16.68% (2)	

*Significance is set at ≤ 0.05

4.2.2 Birth History

4.2.2.1 Birth Weight

The birth weights for the total sample varied between the groups, which received and did not receive induced hypothermia with both having a median birth weight of three kg.

The upper and lower quartile range for the group which received induced hypothermia was lower and fell between 2 and 3 kg while that for the group who did not receive induced hypothermia was between 3kg and 4kg. There was no significant difference in birth weight between the groups (p=0.213) (Figure 4.1).

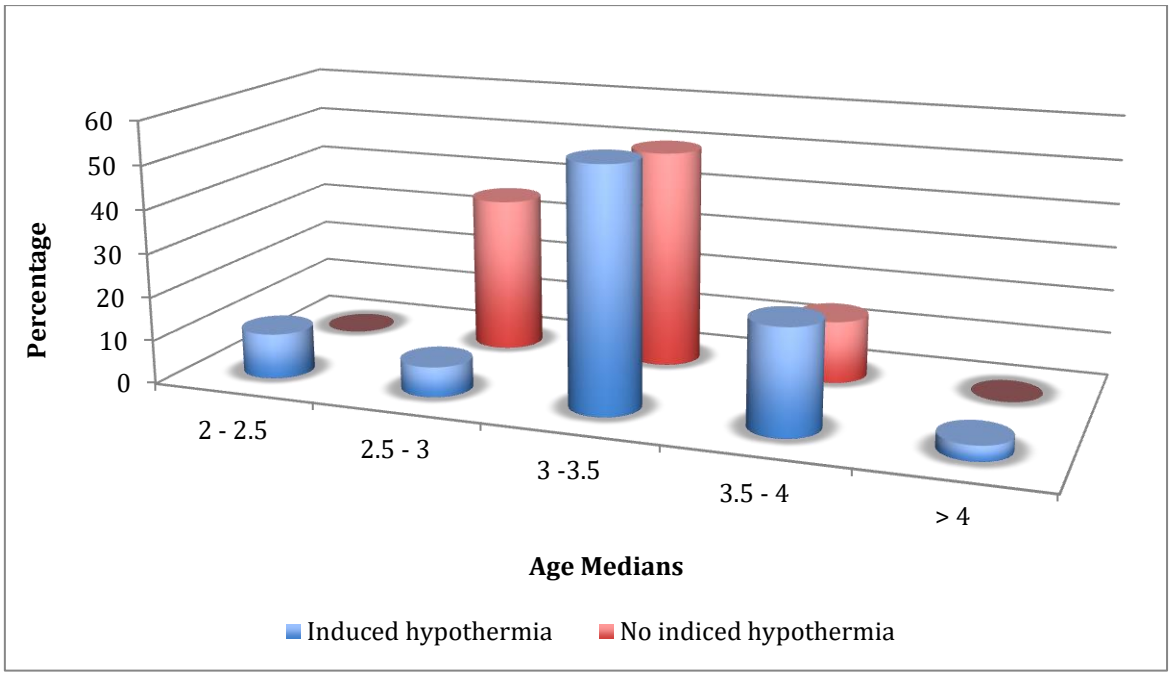

Figure 4.1 Birth weights of infants who did and did not receive induced hypothermia (n=43)

4.2.2.2 Type of Delivery

Significantly more participants who received induced hypothermia were delivered by Caesarean section (p=0.027) but there was no significant difference in those who had some form of assisted birth for the two groups (Table 4.2).

Table 4.2 Type of Delivery and assistance required

		Total sample (n=43)	Induced hypothermia n=29	No Induced hypothermia =14	p value
		Percentage (n = 43)			
Type of Delivery	**Natural vaginal delivery(NVD)**	72.1% (31)	62.06% (18)	92.86% (13)	0.02
	Caesarean section (C/S)	27.91% (12)	37.94% (11)	7.14% (1)	
Assisted Delivery	**None**	83.72% (36)	79.31% (23)	92.86% (13)	0.25
	Vacuum	16.28% (7)	20.69% (6)	7.14% (1)	

*Significance is set at ≤ 0.05

4.2.2.3 Apgar scores

The Apgar scores of the participants who received induced hypothermia were lower than those who did not receive induced hypothermia at one minute (p= 0.540) and at five minutes (p=0.745) but these differences were not statistically significant. A higher percentage of participants without induced hypothermia had achieved Apgar scores above five at five minutes (Figure 4.2).

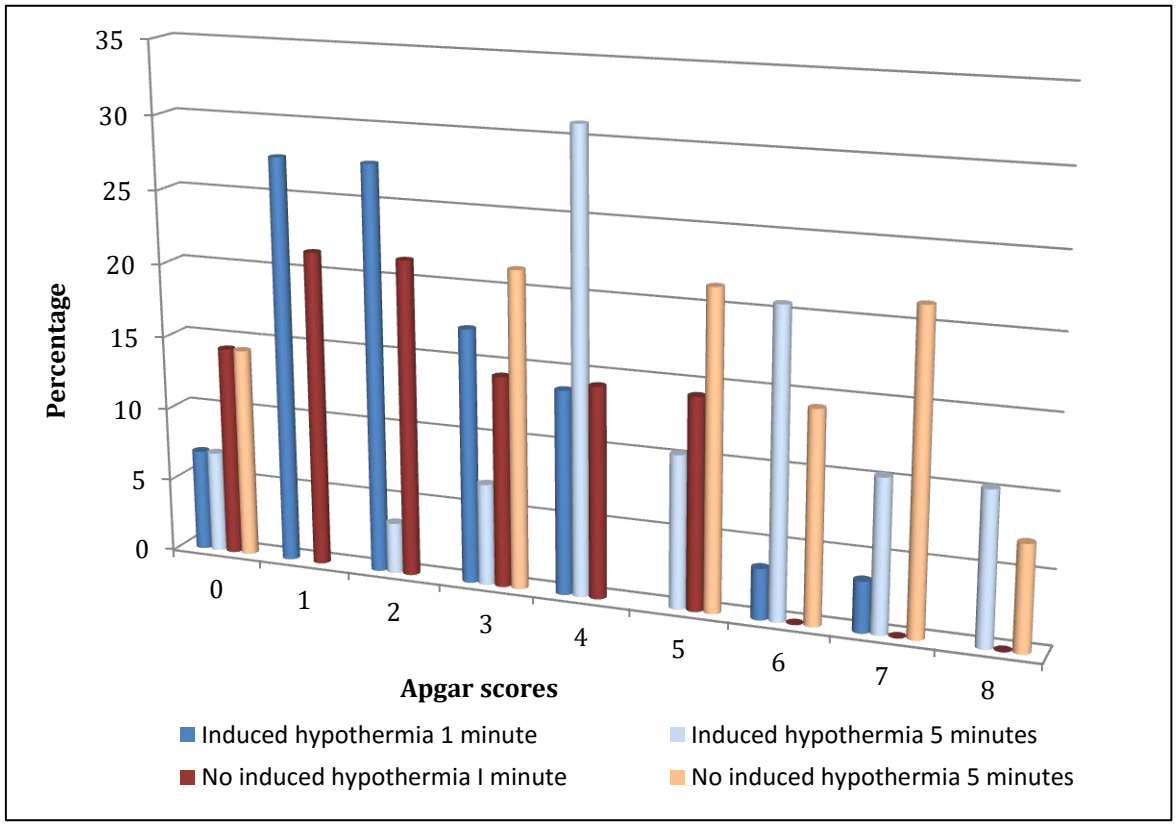

Figure 4.2. The Apgar scores of the participants who did and did not receive induced hypothermia (n=43)

4.2.2.4 Stay in ICU and rehab in the wards

The participants who did not receive induced hypothermia had a shorter stay in transitional intensive care unit (TICU) overall with a median of 4.50 (4-6) days compared to the 7 (3-9) days for the participants who received induced hypothermia. This difference was not, however, statistically significant (p=0.684) (Figure 4.3).

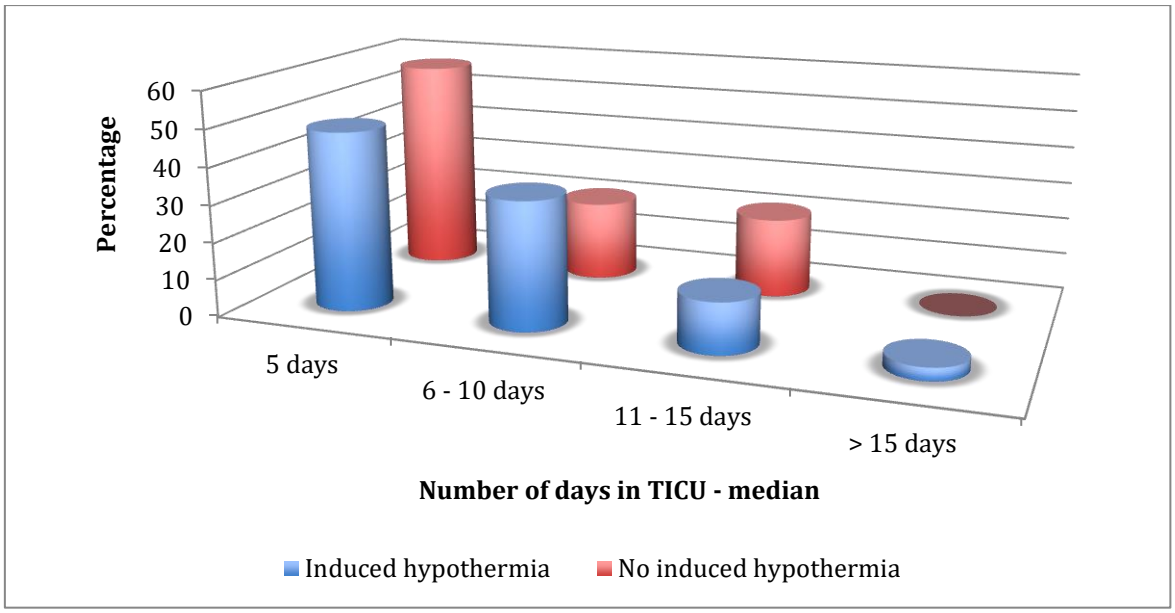

Figure 4.3 Number of days participants who did and did not receive induced hypothermia stayed in TICU (n = 43)

The median for the stay for both groups of participants in the neonatal ward after discharge from TICU was six days (inter quartile range of 05.00 to 09.00) with no significant difference between the groups. TICU is a high care Level Two neonatal care ward. During this time, 6 (24%) of the participants who had received induced hypothermia and 3 (21%) of the participants who had not received induced hypothermia were seen by the transdisciplinary rehabilitation team.

4.2.3 Medical History

4.2.3.1 Diagnosis at Birth - Severity of Hypoxic Ischaemic Encephalopathy

In the study sample, 39 (90%) of the participants presented with HIE II (90%) and 4 (10%) presented with HIE III. Of the four participants with HIE III, three (75%) had received whole-body induced hypothermia. Of the 39 participants with HIE II, 28 (72%) had received induced hypothermia, while 11 (28%) had not.

4.2.3.2 Diagnosis at Birth - Human Immunodeficiency Virus (HIV) Status

The majority of infants were HIV negative (55.8%). Human Immunodeficiency Virus negative means that these infants are unexposed and PCR negative. This is due to the National Prevention of Mother-To-Child Transmission (PMTCT) policy which

addresses the transmission of HIV from mother to child[91]. There were also many infants (25.58%) who were unexposed (their mothers were HIV negative). There was no significant difference between the participants who were unexposed, negative or had an unknown HIV status, when those who had and had not received induced hypothermia were compared (Table 4.3).

Table 4.3 HIV Status of the participants who did and did not receive induced hypothermia (n=43)

	Total sample (n=43)	**Induced hypothermia n=29**	**No Induced hypothermia =14**	**p value**
	Percentage (n = 43)			
Positive	0	0	0	0.83
Negative	55.8% (24)	17	7	
Exposed	9.3% (4)	2	2	
Unexposed	25.58% (11)	7	4	
Unknown	9.3% (4)	3	1	

*Significance is set at ≤ 0.05

4.2.4 Family Demographics

4.2.4.1 Type of Housing

The results show that the majority of participants lived with their families in brick houses or in informal housing. A small number of those that received induced hypothermia lived in Reconstruction and Development Programme (RDP) housing provided by the government to poorer families. There was no significant difference in the housing in which the participants in the two groups lived (p= 0.354).

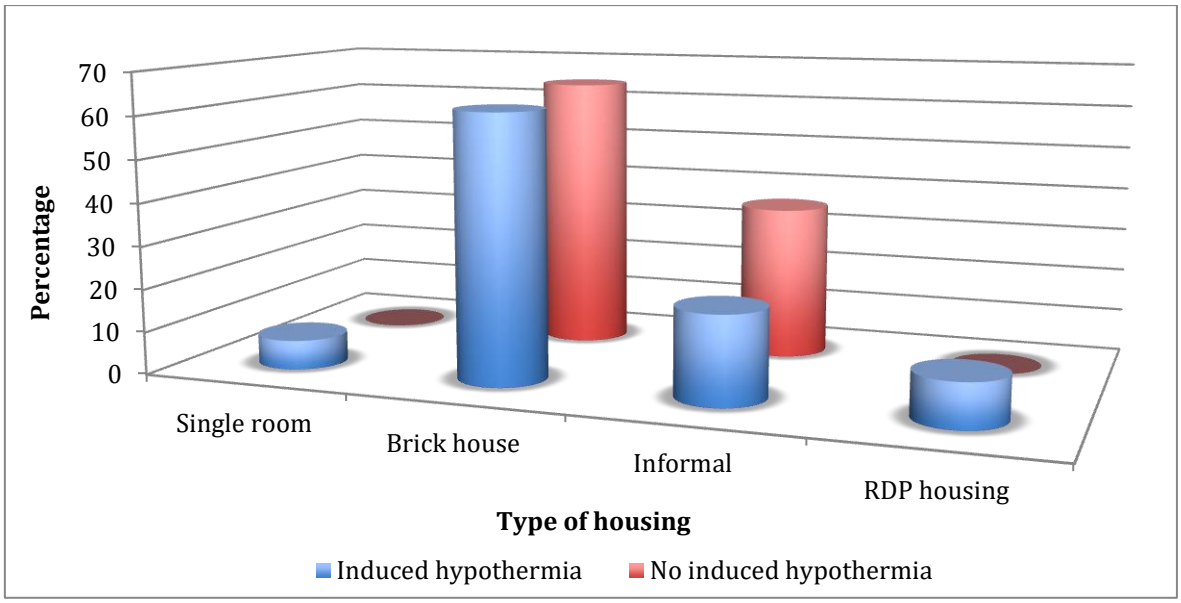

Figure 4.4 Type of house lived in by participants who did and did not receive induced hypothermia (n=43)

In terms of amenities, all the participants' families, with the exception of one, had access to amenities like running water, sanitation and electricity although not all had a water source and sanitation in their homes.

4.2.4.2 Support system

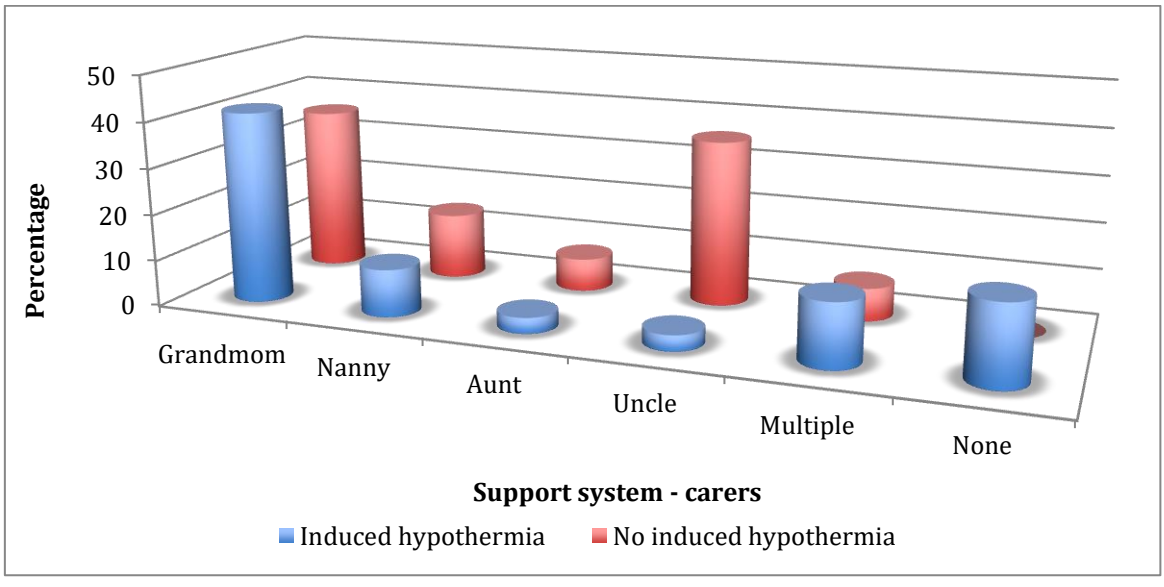

Figure 4.5 Carers of participants who did and did not receive induced hypothermia (n=43)

The majority of participants were cared for by their grandmothers while their mothers were at work. The majority of mothers of participants who did and did not receive induced hypothermia were supported by the infants grandmothers in caring for them. Less than 20% of those participants who had received induced hypothermia had a carer other than their mother or multiple carers (Figure 4.7). In this case, no support system means those children who only have one parent/caregiver caring for them.

4.2.4.3 Income Source

The majority of mothers of the participants in this study were the only member generating income in the family. Only one of the participants received a care dependency grant while about a third of the participants in both groups had child care grants. Very few participants (11.62%) had both parents contributing with an income.

The income sources for the participants who had and had not received induced hypothermia were similar as were the number receiving grants with no significant differences between the groups (Table 4.4).

Table 4.4 Income sources for care of the participants who did and did not receive induced hypothermia (n=43)

	Total sample (n=43)	**Induced hypothermia n=29**	**No Induced hypothermia n =14**	**p value**
	Total sample (n=42)			
Mother	34.88% (15)	34.48% (10)	13.95% (5)	0.90
Father	11.62% (5)	13.79% (4)	7.14% (1)	
Both parents	11.62% (5)	13.79% (4)	7.14% (1)	
Grandparents	6.98% (3)	7.89% (2)	7.14% (1)	
Child support grant	32.56% (14)	31.03% (9)	35.71% (5)	0.20
Child dependency grant	2.33% (1)	0	7.14% (1)	

*Significance is set at ≤ 0.05

The participants who had and had not received induced hypothermia were comparible on the initial assessment for demographic, medical and social factors except for birth mode.

4.3 Comparison of the Bayley–III developmental outcomes of participants who did and did not receive Induced Hypothermia

4.3.1 Baseline Assessment

The developmental assessments of the participants who had and had not received induced hypothermia at baseline were compared using the scaled scores. The Bayley–III have scores that are based on the therapists observations as well as the parents report on behaviour.

4.3.1.1 Therapist observed components of the Bayley–III

Scaled scores for the components of development observed by the therapist (which include cognitive, receptive and expressive language, fine and gross motor function) were compared for the participants who had and had not received induced hypothermia (Table 4.5).

Table 4.5 Comparison of baseline scores for participants who had and had not received induced hypothermia according to scaled scores of the therapist evaluated components of the Bayley–III (n=43)

	Total sample (n=43)	**Induced hypothermia n=30**	**No Induced hypothermia n =13**	**p value**	**Effect size**
	Median (Lower and Upper quartile ranges)				
Cognitive	9 (7-10)	8 (7-10)	10 (7-11)	0.26	-0.25
Receptive language	12 (10-14)	13 (10-14)	12 (11-12)	0.18	0.10
Expressive language	11 (13)	11(9-13)	11 (8-11)	0.18	0.46
Fine Motor	9 (7-12)	9 (8-11)	10.5 (6-12)	0.41	-0.16
Gross Motor	8 (7-9)	8 (7-9)	9 (7-13)	0.28	-0.53

*Significance is set at ≤ 0.05

The baseline assessments were compared, although the participants who had not received induced hypothermia had an overall higher median performance in the areas of cognitive skills, gross and fine motor functioning, these were not significantly different. None of the median scaled scores were below seven which places an infant at risk for developmental delay at the time of baseline assessment for these components. The receptive and expressive language components are higher than all other components for both groups showing that this is the strongest area of development in these participants.

Clinical differences according to moderate effect sizes are relevant for expressive language which was higher for the group who received induced hypothermia and for gross motor scores for the group which did not receive induced hypothermia.

4.3.1.2 Caregiver/parent evaluated components of the Bayley–III

When comparing the caregiver/parent evaluated components it is evident that there is great variability in the social-emotional and adaptive behaviour outcomes as seen below in Table 4.6.

Table 4.6 Comparison of baseline scores for participants who had and had not received induced hypothermia according to scaled scores of the caregiver evaluated components of the Bayley–III (n=43)

	Total sample (n=43)	Induced hypothermia n=30	No Induced hypothermia n =13	p value	Effect size
	Median (Lower and Upper quartile ranges)				
Social-Emotional	8 (5-12)	9 (5-12)	8.00 (1-13)	0.73	0.16
Adaptive Behaviour Communication	10 (7-11)	10 (7-11)	9.5 (7-11)	0.89	0.24
Adaptive Behaviour Community use	8 (7-9)	8 (6-10)	8 (8-8)	0.10	0.00
Adaptive Behaviour Functional preacademics	6.5 (4.5-8)	6 (3-9)	7 (7-7)	1.00	0.33
Adaptive Behaviour Home living	5.50 (5-7)	5 (5-8)	6 (6-6)	1.00	0.00
Adaptive Behaviour Health and Safety	9 (7-10)	9 (7-10)	10 (8-10)	0.82	0.08
Adaptive Behaviour Leisure	8 (5-9)	8 (6-9)	8 (5-9)	0.94	0.02
Adaptive Behaviour Self-care	8 (5-10)	9 (5-10)	8 (7-10)	0.96	0.06
Adaptive Behaviour Self direction	6 (4-8)	7 (4-8)	5 (4-7)	0.64	0.07
Adaptive Behaviour Social	5 (4-7)	5 (4-7)	5 (4-7)	0.84	0.10
Adaptive Behaviour Motor	9 (7-10)	9 (7-10)	10 (9-11)	0.16	-0.13

Overall, more participants had atypical development in both groups particularly in the areas of functional preacademics, home living, self direction and social areas of adaptive behavior. Furthermore, the participants who did not receive induced

hypothermia had lower scores in self care and self direction while the participants who did receive induced hypothermia had lower scores for functional preacademics, home living, health and safety and motor components of adaptive behaviour. The induced hypothermia group had higher scaled scores for the social-emotional components of development as well as the adaptive behaviour components of communication, self-care and self-direction. There were no statistically significant differences between the groups for any scores and no clinically relevant differences were found for any components using effect sizes. Therefore, based on these baseline results participants in both groups were at the same level of development with very few deficits at their baseline assessment.

4.3.2 Reassessment and change in assessment scores for participants who did and did not receive Induced Hypothermia

Participants were followed up at the HIE clinic at CHBAH on a monthly basis. Not all participants attended on a monthly basis and were reassessed when they attended, sometimes up to nine months after the initial assessment. For this reason, the reassessment was done after a period of between three and nine months.

Table 4.7 Comparison of reassessment scores and change for participants who had and had not received induced hypothermia according to scaled scores of the therapist evaluated components of the Bayley–III (n=31)

	Total sample n=31	**Induced hypothermia n=26**	**No Induced hypothermia n =5**	**Difference in score between groups**	**p value**	**Effect sizes**
	Reassess-ment	**Reassess-ment**	**Reassess-ment**			
Cognitive	7 (5-9)	7(5-8)	9(8-11)	-2	0.08	-0.65
Receptive language	10 (7-12)	9(7-12)	11.5 (10-13)	-2.5	0.09	-0.91
Expressive language	9 (6-11)	8(6-10)	10(9-11)	-2	0.36	-0.59
Fine Motor	9 (7-10)	8(7-10)	10(8-11)	-2	0.31	-0.30
Gross Motor	9 (7-11)	9(7-10)	11(9-11)	-2	0.14	-0.38

*Significance is set at ≤ 0.05

At reassessment, scaled scores for both groups showed a decrease for cognition, receptive and expessive language as well as fine motor, whereas, assessment scores for gross motor function improved for both the groups. There was a greater difference in the scaled scores between the groups which did and did not receive induced hypothermia with the group which did not receive induced hypothermia having higher scores in all aspects, three of which were clinically relevant. These were for cognition and receptive and expressive language which had moderate to high effect sizes

In comparing the components evaluated by the caregivers/parents, it was evident that there was more variation in the results. (Table 4.8).

Table 4.8 Comparison of reassessment scores and change for participants who had and had not received induced hypothermia according to scaled scores of the caregiver evaluated components of the Bayley–III (n=31)

	Total sample n=31	**Induced hypothermia n=26**	**No Induced hypothermia n =5**	**Difference in score between groups**	**p value**	**Effect sizes**
	Reassessment					
SE	8(5-11)	8(5-10)	10.5 (9-13)	-2	0.12	- 0.04
AB - Comm	8(6-9)	7(6-9)	9(7-12)	-2	0.25	- 0.22
AB - CU	9(7-10)	9(8-10)	7(6-8)	-2	0.13	0.23
AB - FPA	9(8-11)	9 (8.5-11)	6(5-7)	3	0.04*	0.62
AB - HL	6.5(5-8)	6.5(5-8)	5.5(4-7)	1	0.45	0.10
AB - HS	7(5-9)	7(5-8)	8.5 (7-10)	-1.5	0.26	- 0.25
AB - LS	6(5-8)	6(5-7)	8(7-9)	-2	0.13	- 0.22
AB - SC	5(3-7)	5(3-6)	6.5 (5-8)	-1.5	0.25	- 0.38
AB - SD	5(4-7)	5(4-6)	7.5(4-8)	-2.5	0.12	- 0.19
AB - Soc	5(3-6)	5(3-5)	6(4-8)	-1	0.26	- 0.12
AB - MO	6(4-9)	6(4-8)	8.5 (5-11)	-1.5	0.18	- 0.31

*Significance is set at ≤ 0.05

Key (Table 4.8.):

SE – social-emotional

AB – Adaptive Behavior

Comm – Communication; CU – Community use; FPA – Functional pre-academics; HL – Home living; HS – Health and safety; LS – Leisure; SC – Self-care; SD – Self direction; Soc – Social and MO - Motor

Overall the developmental deficits in both groups became more severe over time. The participants who had received induced hypothermia had higher scaled scores for adaptive behavior components of community use, functional preacademics and home living. The group which had not received induced hypothermia had higher scaled scores of all other components of adaptive behavior as well as social-emotional development

4.3.3 Developmental age scores on the Bayley–III for participants who did and did not receive Induced Hypothermia

In a comparison of chronological age versus developmental age for both groups it was evident that all areas of development decreased on reassessment.

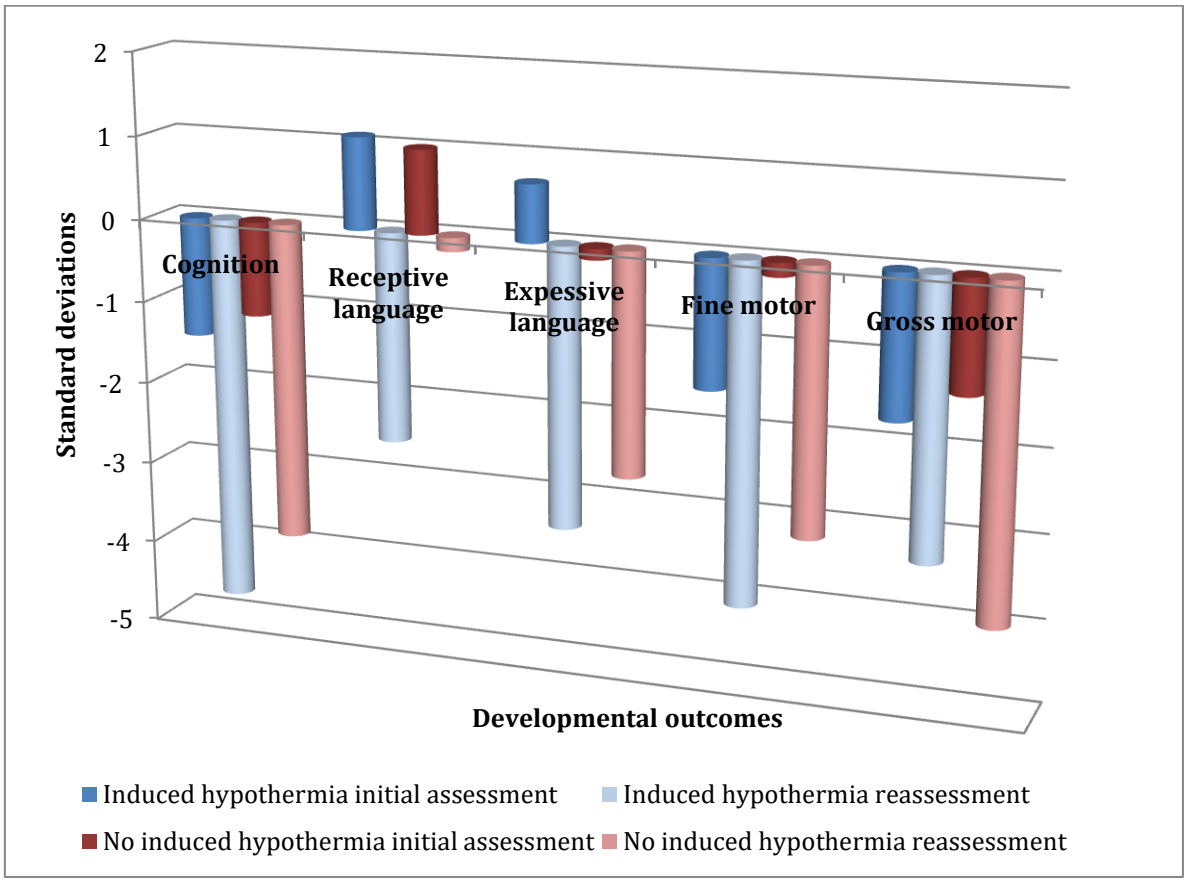

Figure 4.6 Comparison of chronological age versus developmental age at initial assessment and reassessment for participants who did and did not receive induced hypothermia (n=43)

This correlates with the scaled scores presented previously. The mean developmental age scores for cognition, fine and gross motor function were all below those for chronological age.

The developmental age illustrates that of the children assessed before the age of 12 months, 21% were below developmental age initially, while 86% over the age of 12 months were below the developmental age. It appears that the older the child the less likely they are to be at or above developmental age for the total sample. This is not statistically significant but clinically relevant (Table 4.9).

Table 4.9 Change in those scoring at or above developmental age from baseline to final assessment (n = 31)

	Baseline Assessment **< 12 months n=24** **>12 months n=7**	**Final Assessment** **< 12 months n=6** **>12 months n=25**	**p value**
Above developmental age **< 12 months**	(19) 79%	(2) 33%	0.23
Above developmental age **> 12 months**	(1) 14%	(1) 4%	

4.3.4 Component scores of the Bayley–III for participants who did and did not receive Induced Hypothermia

The scaled scores for each subtest assessed by the therapist were analysed according to a normal distribution to establish the percentage of infants who presented with typical development (scaled scores 8-12), were at risk or had mild dysfunction (scaled scores 5-7), had moderate dysfunction (scaled scores 2-4) or had severe dysfunction (scaled score of 1) as shown in Figure 4.9.

4.3.5.1 Cognition

The participants who had not received induced hypothermia had only 7.7% (1 participant) with severe dysfunction, with the majority of infants from both groups

falling into typical or at risk mild dysfunction for cognition. More of the infants (56%) who received induced hypothermia were at risk on reassessment compared to the 52% who showed typical development on the baseline assessment (see Figure 4.7 below).

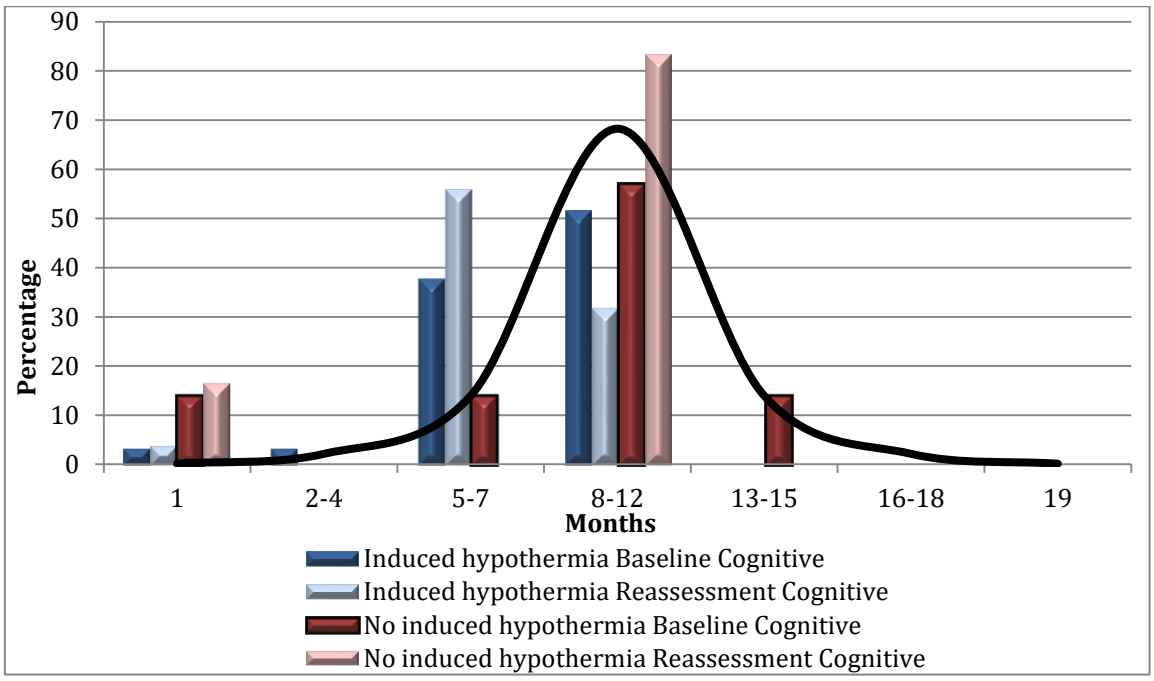

Figure 4.7 Frequency distribution indicating the percentage of children with severe deficits for the therapist assessed components of the Bayley–III – cognitive component (n=43)

4.3.4.2 Receptive language

Similar results to those for cognition were found for the group which received induced hypothermia for receptive language. The group which did not receive induced hypothermia indicated above average development for this subtest with some improvement on reassessment.

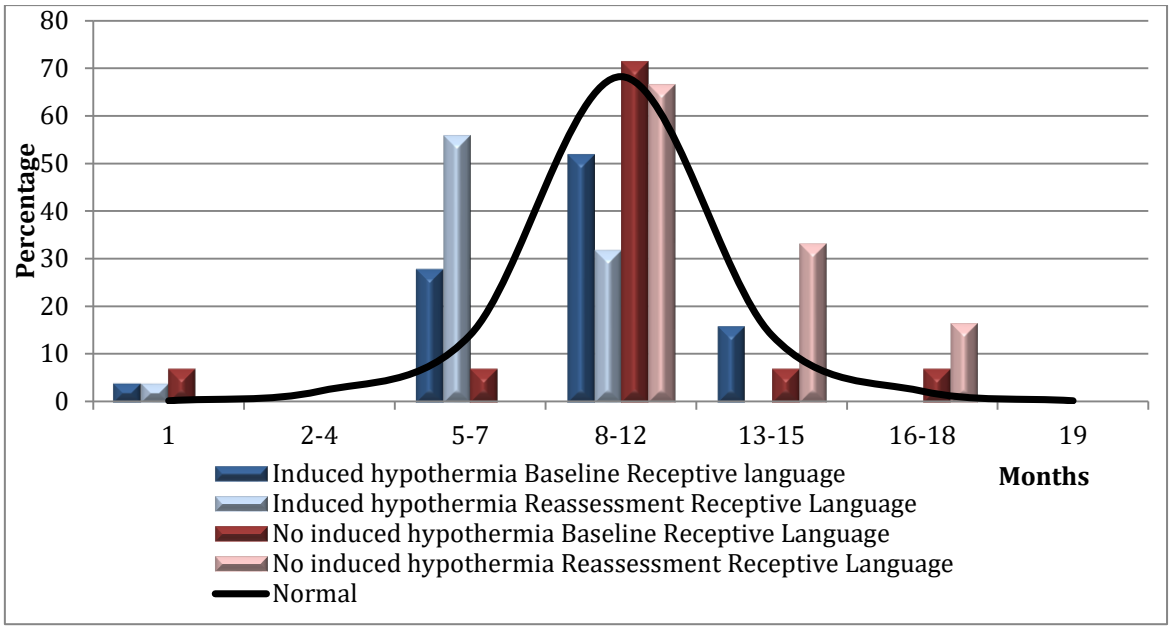

Figure 4.8 Frequency distribution indicating the percentage of children with severe deficits for the therapist assessed components of the Bayley–III – receptive language component (n=43)

4.3.4.3 Expressive language

None of the infants had severe dysfunction in expressive language and a greater percentage fell into the typical performance range.

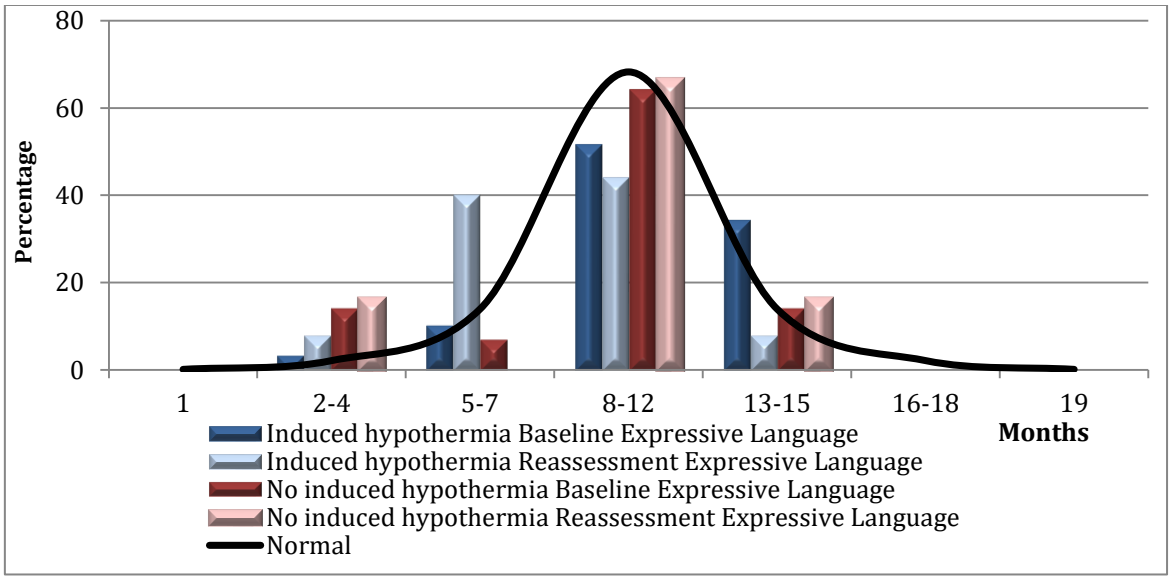

Figure 4.9 Frequency distribution indicating the percentage of children with severe deficits for the therapist assessed components of the Bayley–III – expressive language component (n=43)

The group, which received hypothermia once again, had a greater percentage of infants in the mild at risk group on reassessment (40%).

4.3.4.4 Fine Motor

Infants in the group which did not receive induced hypothermia had 7% with severe dysfunction and 12% of those who did received induced hypothermia had severe dysfunction for fine motor function. In both groups, 72% fell into the typical range of development with 11.6% presenting in the at risk or mild dysfunction category.

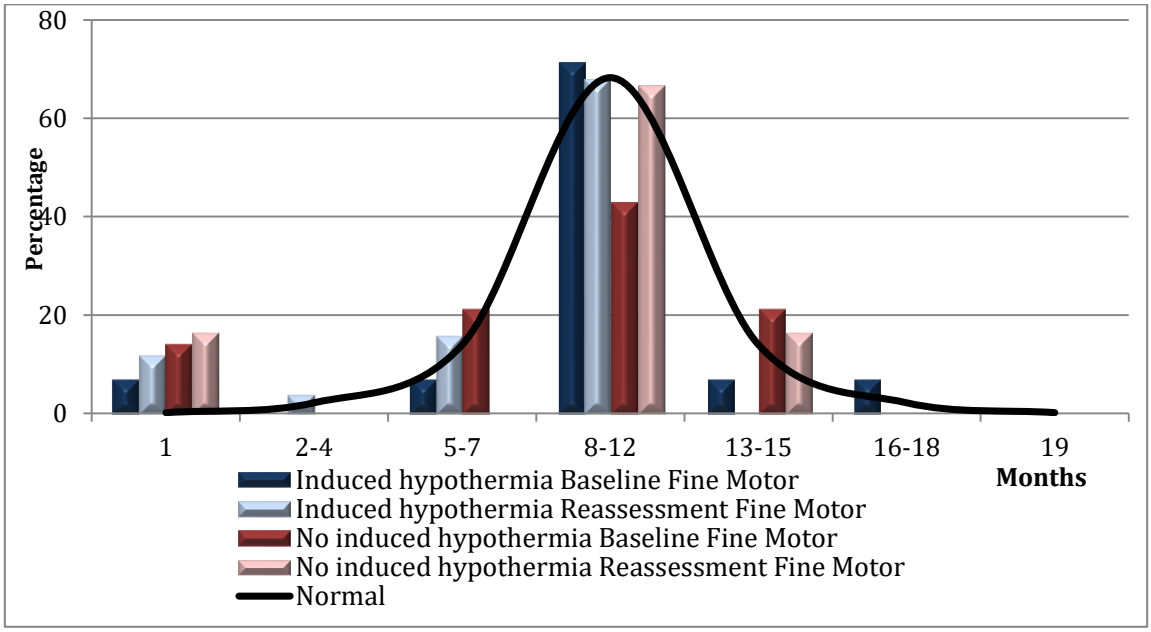

Figure 4.10 Frequency distribution indicating the percentage of children with severe deficits for the therapist assessed components of the Bayley–III – fine motor component (n=43)

4.3.4.5 Gross Motor

A similar number of infants (16%) had gross motor dysfunction with a similar percentage as found for fine motor function having typical gross motor function. Only one infant was in the at risk category on reassessment.

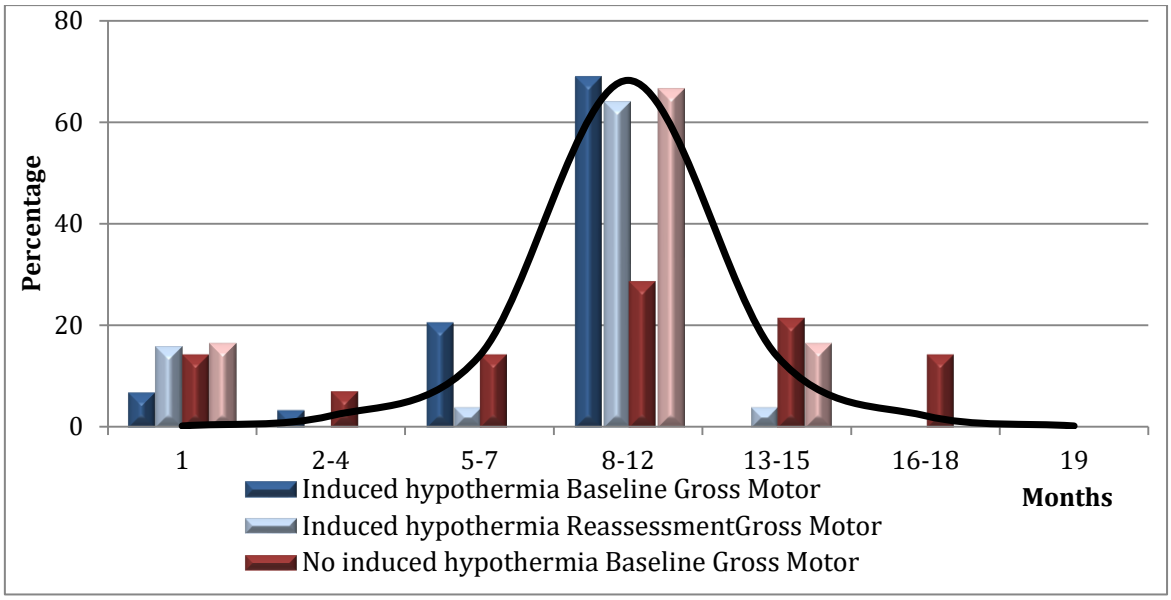

Figure 4.11 Frequency distribution indicating the percentage of children with severe deficits for the therapist assessed components of the Bayley–III – gross motor component (n=43)

4.4 Changes within groups for participants who did and did not receive Induced Hypothermia

4.4.1 Participants who received Induced Hypothermia

Table 4.10 Comparison of initial and reassessment scores and change for participants who had received induced hypothermia according to scaled scores of the therapist evaluated components of the Bayley–III (n=31).

	Induced hypothermia (n=31)			p value	Effect sizes
	Initial asessment n=31	Reassessment n=26	Change in score		
Cognitive	8 (7-10)_	7 (5-8)	-1	0.02*	- 0.22
Receptive language	13 (10-14)	9 (7-12)	-4	0.00*	- 0.38
Expressive language	11 (9-13)	8 (6-10)	-3	0.00*	- 0.45
Fine Motor	9 (8-11)	8 (7-10)	-1	0.26	- 0.11
Gross Motor	8 (7-9)	9 (7-10)	1	0.25	0.04

*Significance is set at ≤ 0.05

There was a statistically significant change within the group which received induced hypothermia for cognitive, receptive language and expressive language components. The score for the fine motor components decreased; however, the gross motor components improved. All scores were below the midline norm but only cognitive skills were in the risk range of seven on reassessment.

Table 4.11 Comparison of initial and reassessment scores and change for participants who had received induced hypothermia according to scaled scores of the caregiver evaluated components of the Bayley–III (n=30)

	Induced hypothermia (n=30)			**p value**	**Effect sizes**
	Initial asessment n=30	**Reassessment n=26**	**Change in score**		
Social-Emotional	9 (5-12)	8 (5-10)	-1	0.36	- 0.13
Adaptive Behaviour Communication	10 (7-11)	7 (6-9)	-3	0.00*	- 0.38
Adaptive Behaviour Community use	8 (6-10)	9 (8-10)	1	0.59	0.29
Adaptive Behaviour Functional pre-academics	6 (3-9)	9 (8.5-11)	-3	0.42	0.78
Adaptive Behaviour Home living	5 (5-8)	6.5 (5-8)	1.5	0.78	0.13
Adaptive Behaviour Health and Safety	9 (7-10)	7 (5-8)	-2	0.03*	- 0.32
Adaptive Behaviour Leisure	8 (6-9)	6 (5-7)	-2	0.02*	- 0.26
Adaptive Behaviour Self-care	9 (5-10)	5 (3-6)	-4	0.01*	- 0.41
Adaptive Behaviour Self direction	7 (4-8)	5 (4-6)	-2	0.04*	- 0.30
Adaptive Behaviour Social	5 (4-7)	5 (3-5)	0	0.51	- 0.17
Adaptive Behaviour Motor	9 (7-10)	6 (4-8)	-3	0.00*	- 0.36

*Significance is set at ≤ 0.05

There was a statistically significant change within the group, which received induced hypothermia for adaptive behaviour components of communication, health and safety, leisure, self-care, self-direction and motor skills. All of these components decreased either showing evidence of risk or developmental deficits. There was no change in the social component or improvement in community use and home living.

There was a low effect size for the cognitive, expressive language, fine motor, gross motor and social-emotional categories as well as the health and safety, leisure, social and motor categories of adaptive behavior. Receptive language and the adaptive behavior categories of communication, self-care and self-direction had a medium effect size.

4.4.2 Participants who did not receive Induced Hypothermia

4.4.2.1 Comparison of initial and reassessment scores and change for participants who had not received induced hypothermia of the therapist evaluated components.

There were no statistically significant changes within the group who did not receive induced hypothermia for any components.. This is shown in table 4.12.

Table 4.12 Comparison of initial and reassessment scores and change for participants who had not received induced hypothermia according to scaled scores of the therapist evaluated components of the Bayley–III (n=13).

	No Induced hypothermia (n=13)			p value	Effect sizes
	Initial asessment n=13	Reassessment n=5	Change in score		
Cognitive	10 (7-11)	9 (8-11)	-1	0.06	- 0.06
Receptive language	12 (11-12)	11.5 (10-13)	-0.5	0.58	0.07
Expressive language	11 (8-11)	10 (9-11)	-1	0.50	0.06
Fine Motor	10.5 (6-12)	10 (8-11)	-0.5	0.40	- 0.04
Gross Motor	9 (7-13)	11 (9-11)	2	0.46	0.03

*Significance is set at ≤ 0.05

As with the group that did receive induced hypothermia all the scores decreased except that for gross motor which showed improvement. All scores on the initial assessment were at midline and above except gross motor function and remained there except for cognitive function which scored a median of 9 on reassessment. Gross motor function improved to above the midline normal score

4.4.2.2 Comparison of initial and reassessment scores and change for participants who had not received induced hypothermia of the caregiver evaluated components.

Overall, the group, which had not received induced hypothermia also had a decrease in the caregiver evaluated components. There was improvement in the social-emotional components as well as the adaptive behaviour components of self-direction and social skills. There was no change in the leisure components of adaptive behaviour.

Table 4.13 Comparison of initial and reassessment scores and change for participants who had not received induced hypothermia according to scaled scores of the caregiver evaluated components of the Bayley–III (n=13).

	No Induced hypothermia (n=13)			p value	Effect sizes
	Initial Assessment n=13	Reassessment n=5	Change in score		
SE	8.00 (1-13)	10.5 (9-13)	1.5	0.75	0.22
AB - Comm	9.5 (7-11)	9 (7-12)	-0.5	0.50	- 0.23
AB - CU	8 (8-8)	7 (6-8)	-1		
AB - FPA	7 (7-7)	6 (5-7)	-1		
AB - HL	6 (6-6)	5.5 (4-7)	-0.5		
AB - HS	10 (8-10)	8.5 (7-10)	-1.5	0.50	- 0.03
AB - LS	8 (5-9)	8 (7-9)	0	0.13	- 0.02
AB - SC	8 (7-10)	6.5 (5-8)	-1.5	0.14	- 0.19
AB - SD	5 (4-7)	7.5 (4-8)	1.5	1.00	0.15
AB - SOC	5 (4-7)	6 (4-8)	1	0.78	0.08
AB - MO	10 (9-11)	8.5 (5-11)	-1.5	0.75	0.08

*Significance is set at ≤ 0.05

Key (Table 4.8.):

SE – social-emotional and AB – Adaptive Behavior

Comm – Communication; CU – Community use; FPA – Functional pre-academics; HL – Home living; HS – Health and safety; LS – Leisure; SC – Self-care; SD – Self direction; Soc – Social and MO - Motor

The adaptive behavior categories of community use, functional pre-academics and home living did not have enough participants to run the test.

4.5 Analysis of the groups with Hypoxic Ischaemic Encephalopathy II and III

Due to the difference in severity of symptoms in the participants diagnosed with HIE II and III, the results for these two groups were compared to establish what differences occurred between them, related to them having received induced hypothermia.

4.5.1 Therapist evaluated aspects of the Bayley–III

All the participants diagnosed with HIE II who had had induced hypothermia fell into scaled scores in the normal range. Language is a strength with this group having a score of more than 10 and cognitive, fine and gross motor being slightly below the midline score of 10 but with no risk of developmental delay. The HIE II group which did not receive induced hypothermia all fell into the normal range according to scaled scores. The HIE III participants who had received hypothermia were at risk of developmental delay for the cognitive and fine motor components.

Table 4.15 Comparison of baseline scores for participants diagnosed with HIE II and HIE III according to scaled scores of the therapist evaluated components of the Bayley–III (n=43).

	Hypoxic Ischaemic Encephalopathy II		**Hypoxic Ischaemic Encephalopathy III**		**p value**
	Median (Lower and Upper quartile ranges)				
	Induced hypothermia n= 26	**No induced hypothermia n=13**	**Induced hypothermia n=3**	**No induced hypothermia n= 1**	
Cognitive	8 (7-10)	10 (8-11)	7 (1-9)	1	0.09
Receptive language	13.5 (10-14)	12 (11-12)	12 (1-14)	7	0.55
Expressive language	11 (10-14)	11 (8-11)	9 (4-10)	4	0.31
Fine Motor	9 (8-11)	11 (7-12)	7 (1-10)	1	0.08
Gross Motor	8 (7-9)	9 (7-13)	8 (1-10)	1	0.09

*Significance is set at ≤ 0.05

There was only one participants with HIE III that did not receive induced hypothermia, this participant was at risk for receptive language delay and had severe developmental delay in the areas of cognition, expressive language, fine motor and gross motor skills.

Participants with HIE II were functioning at the average midline for all components except cognitive on reassessment for the induced hypothermia group. The HIE II participants had an overall decrease in development for both induced and non induced hypothermia groups. There was no change in receptive language for the induced hypothermia group. Improvements were observed in gross motor for the induced hypothermia group and fine motor for the non-induced hypothermia group.

In the HIE III group, all participants from the non induced hypothermia group continued to function at the at risk level for all components of development except for receptive language. Their function remained significantly lower than that of the HIE II group for fine motor only.

Table 4.16 Comparison of reassessment scores for participants diagnosed with HIE II and HIE III according to scaled scores of the therapist evaluated components of the Bayley–III (n=31)

	Hypoxic Ischaemic Encephalopathy II		**Hypoxic Ischaemic Encephalopathy III**		**p value**
	Median (Lower and Upper quartile ranges)				
	Induced hypothermia n= 26	**No induced hypothermia n=13**	**Induced hypothermia n=3**	**No induced hypothermia n= 1**	
Cognitive	7 (5-8)	9 (9-11)	6 (1-8)	1	0.09
Receptive language	9 (7-12)	12 (11-13)	9 (1-10)	8	0.74
Expressive language	8.5 (6-11)	10 (10-11)	7 (3-10)	4	0.44
Fine Motor	9 (7-11)	10 (10-12)	8 (1-8)	1	0.05*
Gross Motor	9 (7-10)	11 (11-11)	7 (1-11)	1	0.09

*Significance is set at ≤ 0.05

The HIE III induced hypothermia group deteriorated in development for all areas except improvement in fine motor. The HIE III non induced hypothermia group did not change but there was improvement in receptive language.

4.6 Summary

In this study, 43 infants with HIE II and HIE III were assessed (4 with HIE III and 39 with HIE II), 67% of these infants received whole-body induced hypothermia. Of these infants 31 infants were reassessed due to loss to follow up.

On analysis of the demographics of the participants, both groups were comparable on initial assessment for demographic, medical and social factors however not birth mode. The majority of infants (32.56%) fell between the ages of five to six months of age and 72.1% were male. According to the inclusion criteria, only children with a birth weight over 2kg were included, the sample had a median birth weight of 3 kg. The majority of infants were delivered naturally (72.1%) but most infants that received induced hypothermia (37.94%) were delivered by caesarean section. The Apgar scores of the infants that received induced hypothermia were lower than those that did not at one minute and at five minutes. The infants who did not receive induced hypothermia had a shorter stay in TICU. The majority (55.8%) of infants were predominantly HIV negative. In terms of family demographics, the majority of infants lived in informal or brick housing with their mothers often being the only member generating income in the family and were often cared for by their grandmothers.

When comparing the developmental outcomes of participants who received and who did not receive induced hypothermia at baseline, it was evident that the participants who had not received induced hypothermia had an overall higher median performance in the areas of cognition, language and motor functioning. Overall, both groups presented with typical development in these areas with receptive and expressive language components being higher than all other components. There is great variability in the caregiver/parent-evaluated components of social-emotional and adaptive behaviour. The participants who received induced hypothermia had higher scaled scores for adaptive behaviour components of self-care, communication

and self-direction as well as social-emotional components. Both groups were at the same level of development with very few deficits at their baseline assessment.

Reassessment results showed evidence that development decreased in both groups for all areas of development excluding gross motor. The group that did not receive induced hypothermia deteriorated, however, overall higher scores were evident in comparison to the group that received induced hypothermia. In spite of the deterioration, both groups still presented with typical development with only the cognitive area of development falling into the at risk category. The caregiver/parent-evaluated components were once again highly variable but correlated with increased developmental deficits in both groups.

When comparing the HIE II and HIE III groups, it was evident that infants with HIE II were functioning typically, although they had an overall decrease in development on reassessment. The HIE III group all functioned at an at risk level for all components, functioning at a significantly lower level for all areas of development.

CHAPTER 5: DISCUSSION

5.1 Introduction

The discussion considers the developmental outcomes of the infants with HIE, who did and did not receive induced hypothermia in this study, in terms of their demographic factors, the antenatal and perinatal factors related to their birth as well as their medical history. The developmental outcomes in terms of HIE II and HIE III are also reviewed briefly in relation to the prevalence at the neonatal clinic at CHBAH.

A comparison of the type of delays in the cognitive, gross motor, fine motor, receptive and expressive language, social-emotional and adaptive behaviour components is discussed for the infant participants with HIE, who did and did not receive induced hypothermia, attending outpatient clinics at CHBAH over a period of between three to nine months. Recommendations for fellow health professionals on considerations for evaluation and intervention for infants with HIE.

5.2 Demographics, Birth and Medical History and Socioeconomic Status

In terms of the demographic factors, the infant participants who did and did not receive induced hypothermia were comparable with no significant difference found for any variable. The infant participants with HIE in the study were predominantly (72%) male (Table 4.1). This incidence for males is a 2% higher than that reported in the literature but the higher incidence of HIE in males is supported by other studies from developed and developing countries[14, 51]. Buckmann and Velaphi (2003) and Padayachee (2015) reported an incidence of HIE in males of 60% and 58% respectively in their South African studies[92 93]. It is evident through other studies into the pathophysiology of neuronal cell death that males are often more at risk not only due to hormonal influences but also due to individual cell properties which have provided perinatal females with a level of neuroprotection against HIE[14, 51].

When considering birth histories, again the group which did and did not receive induced hypothermia were comparable and reflected that described in the literature[94, 95]. While low birth weight does have implications and puts infants at risk

for developing birth asphyxia; studies done in India[95], Bangladesh and Pakistan[94] found that premature infants (< 37 weeks and birth weight < 2000g) were at a higher risk of birth asphyxia, hypothermia, septicaemia, neonatal jaundice and respiratory distress syndrome.[94, 95] All infant participants in this study were at term appropriate gestational age (TAGA). Low birth weight did not play a role in this study as premature infants and those below two kg at birth were excluded. In this study the median birth weight is three kg for both groups (Figure 4.1).

In this study, 21% of the group who received induced hypothermia were vacuum assisted with only 7% of the group who did not receive induced hypothermia requiring this type of assistance (Table 4.2). Therefore when the birth history of the infants in this study was reviewed their mode of birth and assistance at birth placed the group who received induced hypothermia at higher risk of a diagnosis of more severe HIE (Table 4.2). Fawcus and van Zyl (2004) in a study done in South Africa found that post term pregnancy also put an infant at significant risk for HIE[39] while Badawi et al. (1998) reported 69% of risk factors were due to antepartum factors[40]. When risk factors associated with HIE are considered, an important consideration is the mode of delivery. The group who received induced hypothermia presented with a significantly higher rate of caesarean sections (38%) compared to the group who did not receive induced hypothermia (7%) (Table 4.2). This correlates with research by De Vries and Groenendaal[34], Robertson and Perlman[4] and Cowan et al[96] that reports that emergency caesareans as well as assisted vaginal deliveries have an increased risk of HIE[4, 34, 96]. Palsdottir et al. (2007) found a 20% increased risk for HIE in emergency caesarean sections, 6% in forceps assisted deliveries and 22% in vacuum assisted deliveries[37].

An extended low Apgar score at one and five minutes placed the infant participants at higher risk of death or chronic motor disability more so in participants who received induced hypothermia[92] than in the group that did not receive induced hypothermia. The infant participants who did not receive induced hypothermia (62%) had a median Apgar score of above five at five minutes, and although this was not statistically different from the group which did receive induced hypothermia (Figure 4.2) according to the criteria developed by ACOG and AAP they were less at risk as they did not have extended low Apgar scores after five minutes[10, 25, 97] (Figure 4.2).

In this study, even though some participants were exposed to factors placing them at a higher risk for HIE such as length of stay in TICU there was no statistically significant difference for those who received induced hypothermia and those who did not. The participants who did not receive induced hypothermia had a shorter stay in the ICU with a median of two and a half days less than the group who did receive induced hypothermia (Figure 4.3). The median for both groups of infants in the neonatal ward was 6 days, which appears to be typical for a large academic hospital in South Africa as it is similar to a mean of 6.5 days in the neonate ward reported for surviving infants in Charlotte Maxeke Johannesburg Academic Hospital[93]. The maximum stay for participants in this study, between 13-15 days for the two groups, was also comparable to a study done in Nigeria in 2013 where infants with HIE had an average hospital stay of 3.8 ± 4.12 days with an 18 day maximum[46], compared to the median of 10 days in the United Kingdom[31] and 13 days in Sweden[37].

In this study, the assessment of severity of HIE was done using the Sarnat grading criteria and the Thompson score as they are easily accessible, use clinical symptoms and are appropriate for use in developing countries[3, 48]. These criteria take into consideration additional medical history.

When the severity of HIE was considered in this study there were only four infants with HIE III (10%), three of these infants received induced hypothermia. Of the 39 infants with HIE II, 28 received induced hypothermia (72%).

Only 10% of the sample (four out of 43 infants) were diagnosed with HIE III. This prevalence is lower than that 23,7% reported before the introduction of induced hypothermia, in a similar study carried out at CHBAH in 2013 by Sukha (2014)[43]. The smaller number of infants diagnosed with HIE III in the HIE clinic may reflect the increase in infants receiving induced hypothermia[34, 42, 51].

Literature indicates a decrease in the incidence of HIE at CHBAH from 2009 (8.3/1000 live births) to 2007 (9/1000 live births). These figures are higher than those reported in the literature for HIE even for developing countries and South Africa. It is further reported that developing countries have an incidence of HIE of 4.6/1000 live births with 2.7/1000 with moderate and severe HIE[10, 53]. Bruckmann

and Velaphi (2011) found an incidence of 3.6/1000 live births of HIE II and 1/1000 for HIE III[10, 53, 92, 98].

When considering other risk factors for developmental delay, HIV and socioeconomic status must be considered in the South African context[91]. This is clearly evident in this study as the majority of infants were HIV negative (55.8%) as well as unexposed (25.6%), meaning that their mothers are HIV negative, with none of the infants being HIV positive (Table 4.3). An infant is considered unexposed to HIV if their mother is HIV negative and the infant is considered HIV negative if they are polymerase chain reaction (PCR) negative. Therefore it can be assumed for the infant participants in this study that HIV will not be a compounding factor in their development or developmental delay.

The infant participants' financial and social support was considered in this study since studies have found evidence that socioeconomic status affects an infant's risk of HIE[40, 91, 99]. All the infant participants came from a low to low middle socioeconomic status, and most of the infants lived with their families or caregivers in informal housing or brick houses. Most families had access to all amenities i.e. electricity, water and sanitation although not always within the house (Figure 4.6).

The low socioeconomic status of the families meant that the majority of mothers were breadwinners (35%) and were often the only member generating income within a family. Grandmothers therefore cared for the majority of infants and if not cared for by their grandmothers, their mothers received most of their support from the grandmothers in caring for them (Figure 4.7). This will have an impact on the infant's development as grandmothers often have difficulty executing the home programmes due to fatigue, time constraints with multiple grandchildren requiring care and limited resources i.e. caring for infants with pension as their only form of income.

Only a third of infants received child support grants (R330 per month) provided to indigent parents with only one infant receiving a care dependency grant (R1410 per month). Care dependency grants are approved for those infants that require additional support i.e. multiple hospital visitations and requiring additional care (Table 4.4)[100]. These factors influence an infant's neurodevelopment as their mothers are often working or have minimal support. Consequently, little or no stimulation is

provided to these infants. Limited resources also make it difficult for the parents/caregivers to provide these infants with adequate stimulation.

The effect of socioeconomic status, culture, level of education and available resources are all critical elements that need to be considered in relation to the composite scores for the participants at CHBAH. However, their scores were similar to the 99.7 for cognitive, 106.8 for language and 103.5 for motor found for a sample of 122 typical black African infants, between three and 12 months, from an urban area in Johannesburg, South Africa[70]. The slightly lower scores can be accounted for by the small percentage of participants with severe disability.

5.3 Developmental Outcomes for Participants with Hypoxic Ischaemic Encephalopathy

The first objective of this study was to consider the developmental outcomes of a sample of infants with HIE who underwent induced whole-body hypothermia versus those who did not, all seen at CHBAH neonatal clinic between 2014 and 2015.

After the initial assessment, 72% of infants returned for reassessment within the 12-month period of the study. In other studies[49, 54,102] it was evident that 79% of infants returned for follow up at a 6-month period, which is in keeping with this study. It is important to note, however, that in the study by Sukha (2014) at CHBAH, a 54% return for follow up services was achieved which is lower than this study[43].

There are a number of factors that could be responsible for this increase in compliance in this study. There has been a change in the clinics from previous years where all infants who were at risk of developmental delay including premature infants were all followed up at one follow up clinic, this made it quite easy for some HIE infants to get missed amongst all the other delayed children. Currently, all HIE infants are followed up at the HIE clinic and are followed up by neonatologists with specialized training in neurology to ensure that these infants are followed up more effectively.

5.3.1 Composite Scores on the Bayley Scales of Infant and Toddler Development – 3rd Edition

5.3.1.1 Introduction

In this study at the baseline assessment, 74.6% of the total sample presented with typical development or scaled scores above seven. Thus their development can be considered as close to that of their typical peers of similar age for both the induced hypothermia and non-induced hypothermia groups.

5.3.1.2 Overview of development according to composite scores

Participants who were identified at risk of developmental delay are those with scaled scores of five to seven or -1 SD below the mean. Those with moderate disability were those with scaled scores of four or less or –2 SD below the mean and those with severe developmental deficits had scaled scores of one or -3 SD below the mean. In this study, 15.8% of infant participants presented with developmental components at risk and 9.6% of the total sample presented with moderate and severe developmental deficits.

On reassessment, between three to nine months later, it was evident that the infants development level had decreased with more deficits becoming evident, with 24.6% of infant participants now showing evidence of being at risk for developmental delay and 11.6% with moderate or severe developmental deficits. The exception to this was gross motor development, which improved for both groups. It is possible that this is related to the pathophysiology of HIE and the patterns of brain injury that occur in HIE. From clinical experience it has been observed that parents often find it easier to provide exposure and stimulation with regards to motor development within limited resource contexts. Consequently, the infants presented with less developmental delay in their motor skills in comparison to other areas of development.

While the group that did not receive induced hypothermia had slightly higher scores in all areas of development, both groups were on par developmentally. The group that received induced hypothermia showed evidence of deterioration in their scores to a risk level (-1 SD below the mean) in cognition, expressive language and gross motor on reassessment, less than 20% of the participants presented with moderate to severe delay according to developmental ages. This is still lower than percentages reported for severe disability noted in other studies[44, 49, 58].

Chalak et al., using the Bayley-III with 90 children with HIE in tertiary institutions in the USA, found that 50% of children presented with composite standard scores >85 indicating normal development in cognitive, language and motor components. Thirty seven percent (37%) of children were at risk of developmental delay and 13% presented with standard scores <70 demonstrating moderate to severe delays[81].

The median composite scores found for this study were also all above 85 (equivalent to a scaled score of 7 or -1SD) and ranged from 92.5 for cognition, 109 for language, 94 for motor and 90 for social-emotional, except for 82 for adaptive behaviour. These scores were due to more than 70% of infant participants in this study at baseline and at reassessment having a score above 85. Overall, the percentage of participants with developmental delay was lower in this study, although the percentage with severe delay was similar to that reported by Chalak et al[81].

5.3.1.3 Severity of disability according to composite scores

At the baseline assessment, 11.4% of the participants who did receive induced hypothermia presented with moderate or severe disability whereas 9.2% of the participants who did not receive induced hypothermia presented with moderate to severe disability. Due to various resource limitations (i.e. shortage of machines), some neonates who meet the criteria to receive induced hypothermia may not receive the treatment. These results must therefore be viewed in light of the resource constraints at CHBAH, even though the modified TOBY criteria used for selecting appropriate infants for receiving induced hypothermia are based on the following best practice standards described by Azzopardi et al[59]. Not all infants requiring induced hypothermia can be accommodated.

Unlike the majority of other studies[15, 26, 36]reporting on the results of induced hypothermia, the rates of moderately or severely disabled children was slightly higher in the induced hypothermia group in this study both at baseline and on reassessment[44]. Infants at CHBAH are often prioritised according to the severity of asphyxia, which may indicate that participants with more severe symptoms received induced hypothermia or according to the first come principle. Infant participants with more severe symptoms may have received induced hypothermia, which may account for the greater developmental delay seen in this study for these infants in this

context. The difference in the percentage of children with moderate to severe disability who did and did not receive induced hypothermia in the TOBY trial was also small as is the case with this study[64].

A difference between this study and the TOBY trial and other studies was found to be reporting on the use of induced hypothermia in HIE in the percentage of children who presented with moderate to severe disability. In the TOBY study in 2009, 33% of children who received induced hypothermia had moderate to severe disability while 30% of children who did not receive induced hypothermia presented with moderate to severe disability. The rate of moderate to severe disability reported by Simbruner et al. was 60% in the group who did not receive hypothermia whereas for the group who received induced hypothermia group it was 21.2%, lower than that reported by TOBY[44, 64].

The above finding was further supported by a review of earlier trials by De Vries and Groenendaal where they found 36% (111 out of 311) of children had moderate or severe neuromotor delay (-2SD below the mean) when assessed on the BSID II. The children who had received induced hypothermia had a notable reduction in the neuromotor delay, however this was not statistically significant when compared to those who had received induced hypothermia[34]. The findings in this study were similar, there are no statistically significant differences for development on any of the therapist observed and caregiver reported subtests on the Bayley III for participants who did and did not receive hypothermia, with the exception of adaptive behaviour pre academic development on reassessment (Tables 4.5 -4.8).

5.3.2 The Subtests of the Bayley Scales of Infant and Toddler Development III for participants who did and did not receive Induced Hypothermia

The second objective was to determine and compare the developmental outcomes of infants with HIE who had and had not received induced hypothermia and the change that occurred over time after attending a transdisciplinary early development programme at CHBAH. Each subtest of the Bayley–III was considered separately in terms of the development of the participants who did and did not receive induced hypothermia in this study.

5.3.2.1 Motor Development

The median composite score for motor abilities is 94 for the total sample at baseline and on reassessment, which is considered a typical developmental score. This indicates that the majority of these participants fell within a typical range. The study by Chalak et al. (2014)[81] on the Bayley–III which assessed the outcomes of term infants after receiving induced hypothermia therapy, found an average composite score of >85 (normal/no delay) which supports the findings of this study.

When considering gross motor components in this study, 13.5% of participants overall presented with severe deficits and 2.6% with moderate delay in their gross motor component of development while 9.8% were at risk of developmental delays. These findings showed less developmental delay than those reported by Sukha (2014) in her study completed at CHBAH on participants with HIE before induced hypothermia was introduced. She found that a lower percentage of infants (50%) had no disability in their gross motor function whereas in this study the percentage was 71.1%. This shows that infants were at less risk and had fewer deficits in their gross motor skills after the introduction of induced hypothermia in this study. Sukha also found just over 28.0% presented with severe disabilities and 9.3% presented with moderate disabilities for this component using the Peabody Development Motor Scale (PDMS)[43].

When the groups were compared for gross motor development the median scaled scores for the group, which did not receive induced hypothermia, were higher (Table 4.5) at a scaled score of 9 in comparison to the group that received induced hypothermia with a score of 8. The lower percentage of moderate and severe disability seen in this study (even in the group that did not receive induced hypothermia) appears to confirm the assumption that the infants with more severe hypoxia are receiving induced hypothermia.

When comparing the change over time within the groups of participants who received induced hypothermia (Table 4.10), moderate and severe delay was lower (10%) than the group who did not receive induced hypothermia (21%). On reassessment, the participants presenting with severe delay were nearly equal at 16% and 17% respectively with no participants with moderate delay. Overall there

was improvement in gross motor skills in both groups however the group that did not receive induced hypothermia had greater improvement in gross motor skills (change of 2 in comparison to 1) (See Table 4.10 and 4.12). The difference between the groups was clinically relevant at baseline with a moderate effect size but the small effect size no longer showed clinically significant differences between the groups on reassessment (Table 4.10 and 4.12).

In conclusion, the participants in this study were predominantly on par for their gross motor skills. Gross motor skills improved over time in the participants, this may be related to the home programme provided by the transdisciplinary therapy team.

On analysis of fine motor skills in this study including the scaled scores and developmental ages, it was evident that the fine motor skills were within an average range on assessment and decreased on reassessment for both groups. Overall, at baseline assessment the median scaled score for fine motor skills was 9 with the induced hypothermia group having a lower median score of the group that did not have induced hypothermia with a score of 10.5 (Figure 4.5). Fewer participants presented with moderate (1%) and severe (12,5%) deficits as well as at risk (11.1%) fine motor skills when compared to the findings by Sukha (2014)[43]. Her study showed 25.3% of infants presented with severe dysfunction and 15.3% with moderate dysfunction with object manipulation and grasping. She found a lower percentage of infants (38%) fell into the normal range[43] compared to the 75.3% in this study. It must be remembered that Sukha used a different developmental assessment, but even so, both tests used in her study and this one are norm referenced. It can thus be assumed that a higher percentage of participants presenting within a normal range may be due to the increase in number of infants with severe asphyxia receiving induced hypothermia.

Change within the groups from baseline to reassessment showed an overall decrease in fine motor scaled scores, however, these scores still fell into a normal range. The scaled scores for the group who did not receive induced hypothermia remained the same (Figure 4.5) and a median score was an average 10 on reassessment (Table 4.12). The group who had received induced hypothermia had a decrease in skills on

reassessment; however, this was only borderline with a scaled score of 8 (Table 4.10). The percentage of participants with severe delay increased for both groups with a greater increase in the group who had received induced hypothermia.

When comparing the participants who had and had not received induced hypothermia again, nearly 70% of participants in both groups fell within the average range. Although there was no statistically or clinically significant difference between the groups for fine motor function at baseline, the percentage of participants who received induced hypothermia with moderate (4%) and severe delay (7.1%), was also lower than the group which did not (16% severe delay) at baseline (Table 4.5).

Both groups showed an increase in the percentage of participants with severe delay on reassessment particularly in the group, which received induced hypothermia (12%). As for gross motor function only participants in the group who did not receive induced hypothermia had above average scores therefore, when the groups were compared for fine motor development the median scaled scores for the group who did not receive induced hypothermia was higher (Table 4.5).

For both gross and fine motor development, the percentage of participants with severe deficits was below 20% showing deterioration in function according to developmental age as well.

In conclusion, the majority of the participants scored within an average range for gross and fine motor skills. An area of concern is the deterioration in fine motor skills over time particularly in the group that had not received induced hypothermia.

5.3.2.2 Cognitive Development

5.3.2.2.1 Overall cognitive development at baseline and reassessment

Cognitive development for the majority of participants in this study was found to be within a typical range in both groups with a median composite score of 92.5 at baseline. On reassessment the cognitive composite score decreased to a median of 85 which is a borderline score indicating that the infants were at risk on reassessment. This correlates with a study on cognitive and behavioural consequences by Handel et al. (2007) that found lower intelligence scores but still normal ranges within a group of children with moderate neonatal encephalopathy. There have, however, been

specific deficits noted in older children in terms of spelling, reading and arithmetic/mathematics[54, 11].

The lower cognitive composite scores in comparison to motor scores reflect other studies where there was evidence that cognitive deficits occurring in the absence of motor deficits and cerebral palsy after perinatal asphyxia[101, 102, 79, 84]. The risk of this is dependent on the pattern of brain injury as well as the severity of encephalopathy[102,84].

The change in the median cognitive composite score in this study had a moderate effect size, which made it clinically relevant. The change may be related to the difficulty of assessing cognitive development in infants under 12 months old. In a study by De Vries and Groenendaal (2010), cognitive deficits were recognizable when children with watershed patterns of injury were assessed at 30 months which were often overlooked at 12 months[34, 85]. From clinical experience, the researcher is aware that cognitive skills are more difficult to stimulate in contexts with limited resources and are more often dependent on level of education of the caregiver as well as resources. This may account for some of the change seen in this study.

5.3.2.2.2 Comparison of the group that received induced hypothermia and the group that did not.

Other within group changes indicated that at baseline, the percentage of participants who did not receive induced hypothermia with severe delay was higher (14%) than the group who did (3.4%). At reassessment, there was no change in the number of participants with severe deficits. This is in contrast and lower than a study done by Shankaran et al (2005) that used the Mental Development Index (MDI) of the BSID–II showing an 18% rate of moderate and severe cognitive deficit (MDI <70) in a group which received induced hypothermia versus 22% of the non-induced hypothermia group[58]. This could be due to a discrepancy between BSID-II and Bayley-III. Studies have shown that the cognitive scores of the Bayley-III are significantly higher than the BSID-II equivalent[103, 104].

It was evident that both groups showed deterioration in cognitive skills on reassessment (Table 4.9 and 4.11) although there was only a significant decrease (p=0.02) for the group who received induced hypothermia. The median score for the

induced hypothermia group dropped to seven (Table 4.10), which confirmed the majority of participants of the group that received induced hypothermia were at risk and that in this group participants had a greater deterioration in their cognitive skills.

When comparing the cognitive components between the groups in this study, it was evident that 9% of participants overall presented with severe deficits with the highest percentage for therapist assessed components (30%) being at risk of developmental deficits/delays in cognitive development. Although the difference between the groups was not statistically significant at baseline and reassessment, the moderate effect size at reassessment showed a clinically relevant difference between the groups for cognitive development (Table 4.5).

This is then further evidence that infants who are not afflicted by severe disabling conditions after neonatal encephalopathy present with subtle impairment at a later stage particularly in terms of their cognitive function. Should an infant with HIE survive they are at higher risk of resultant conditions such as profound intellectual impairment and cerebral palsy which are easily recognizable, but disabilities such as mild intellectual impairment, subtle learning disabilities and language impairment may go unrecognized[7, 13].

This study shows that there is a possible deterioration in cognitive skills over time and that these skills need to be evaluated. These children need to be carefully assessed and monitored with information provided to their parents/caregivers on detecting cognitive deficits.

5.3.2.3 Language Development

5.3.2.3.1 Comparison of language skills to other components of development

In this study the language components of receptive and expressive language were significantly higher than all other components and were the strongest components overall with scaled scores of 12 for receptive and 11 for expressive language for both groups. This correlates with the SA study by Rademeyer and Jacklin (2013) which also had higher language scores in their sample in comparison to US norms particularly between the ages of two and 10 months[70], this was the period that the initial assessments were conducted in this study.

5.3.2.3.2 Comparison of overall language skills at baseline and at reassessment

The median composite score for language abilities in this study is 109 at baseline; this is considered a normal developmental score. This median score indicates that on baseline and on reassessment these participants fell within the typical range. This is higher than both the SA study done in 2013 on typical children (106.8)[70] as well as the UK study by Johnson et al. in 2014 (CS =103.2)[68] on typical children. This finding provided evidence that language skills of children with neonatal encephalopathy are less affected than the other areas of development, and even though the median composite score decreased on reassessment, it remained at a typical score of 100.

5.3.2.3.3 Comparison of receptive language components at baseline and at reassessment

When considering the receptive language components of the group, which received induced hypothermia at baseline, only 4% of participants presented with severe deficits and 28% are at risk of developmental delays at baseline. On reassessment, the percentage of participants at risk had increased to 56%. This change was statistically significant (p=0.00) and the median score dropped from above average (13) to average (9) with only 32% of participants still falling in the normal range of development.

For the group which had not received induced hypothermia, the percentage of participants with severe deficits and at risk was 7% respectively. The percentage of participants in the normal and above average range for receptive language in this group was over 80% at baseline and on reassessment. No participants in either group had moderate delay.

When the groups of participants who had and had not received induced hypothermia were compared, no significant difference for receptive language was found and although there was no clinically relevant difference at baseline according to the small effect size, the difference was clinically relevant on reassessment with a large effect size. This indicates a level of deterioration in the participants who had received induced hypothermia in relation to those that had not. It is vital therefore that these participants receive further assessment and follow up in terms of oral-motor-

dyspraxia, language disorders or auditory processing disorders[4] to monitor their development.

5.3.2.3.4 Comparison of expressive language components at baseline and at reassessment

Delay in receptive language is related to delay in expressive language and therefore the pattern of delay for expressive language in these participants was similar with slightly less delay, to that described above. No participants in either group were found to have severe deficits in expressive language, and fewer participants in the group which received induced hypothermia, both at baseline (<1%) and on reassessment (8%) had moderate deficits compared to the participants who had not received induced hypothermia (the percentage was 14% for both assessments). Although 80% of participants showed no developmental delay in this component at baseline, the change at reassessment was once again significant (p=0.00) for the group, which received induced hypothermia. The median score for this group dropped from 11 to 8 and while this was still in the normal developmental range, 40% of the participants were at risk of delay on reassessment.

When the groups were compared, the participants who received induced hypothermia had a higher range of scores for expressive language with a moderate effect size indicating that this was clinically relevant. The situation was reversed on reassessment where the deterioration in the level of development of this group meant the participants who had not received induced hypothermia had higher scores, which were clinically relevant. There was no statistically significant difference between the groups.

The decrease in language scores can be explained by the increased age of the participants on reassessment in this study, as was the case when Rademeyer and Jacklin (2013) found differences in composite language scores in typical South African children on the Bayley-III. They found that the scores were significantly higher (p=0.001) at six months than they were at three months as well nine months of age[70]. This is also supported by Shankaran et al. (2012) as their study provided evidence that children who are not severely disabled due to neonatal encephalopathy will have language deficits at a later stage[97].

This discrepancy in scores on the Bayley-III does not account for the significant decrease in developmental level seen in the group who received induced hypothermia where change seems to be related to cognition. No published studies on language development per se in HIE could be found but Carson et al. (1998) reported an association between receptive and expressive language and cognitive development.[75] Since these results for language closely reflect those for cognition this association needs to be further investigated.

5.3.2.4 Social-Emotional Development

Very limited literature on the social-emotional skills and development of children with Hypoxic Ischemic Encephalopathy has been published and therefore minimal comparisons could be made. The social-emotional median composite score in this study fell into the normal developmental range and the median score was 90 at baseline and on reassessment which is lower than that reported in a study done in Spain on children with HIE where the composite score was 101.6[105]. An important consideration when comparing these two groups is culture, language and socioeconomic status. A lower socioeconomic status can be linked to lower social-emotional scores. Research on the Bayley-III in South Africa on black urban children shows they function around the average scores for motor, language and cognitive function but did not review the parent/caregiver reported aspects. The effect of socioeconomic status and culture on these scores is thus unknown[70].

The social-emotional components on the Bayley-III are evaluated by parents/caregivers and in this study there was an average scaled score of 8 at baseline and at reassessment. In this study 23% of participants presented with moderate and severe deficits and 19% were at risk for delayed development. The change within the group who received induced hypothermia showed a non-significant decrease while the group of those who did not receive induced hypothermia showed a non-significant increase in social emotional behaviour.

When the groups were compared there was no statistically significant difference between them. Those who had received induced hypothermia had 20% of participants with moderate deficits and 25% of those who had not received induced hypothermia had moderate deficits. Over 70% of participants in both groups were

reported to have normal or above average development in this component. These results probably reflect the cognitive and language component results found in this study, as social emotional behaviour is associated with development in these components[102].

Badawi et al. (2006) found that children with neonatal encephalopathy have a higher risk of autism spectrum disorder (ASD) than typically developed peers of the same age. No studies on the use of the Bayley-III in the social emotional evaluation in the identification of children with ASD associated with neonatal encephalopathy were found. It is important for participants within the severe deficit category, to be assessed by practitioners in order to identify if they are at risk for autism to ensure earlier diagnosis for earlier intervention[106]. Determining the most appropriate tool for this requires further investigation.

5.3.2.5 Adaptive Behaviour Development

5.3.2.5.1 Overall adaptive behaviour development

Adaptive behaviour measured by the Bayley-III makes use of the General Adaptive Composite (GAC) score, which provides an overall measure of the child's adaptive development. The GAC for the overall group in this study was 82 at baseline assessment indicating moderate deficits in adaptive behaviour. This correlates somewhat to a review done by Van Handel et al., which reported parents/caregivers opinions on their children's behaviour and found problems with aggression, tractability, anxiety and passivity[54]. This score decreased to 76, indicating at risk behaviour on reassessment.

In total, the adaptive behaviour component of the Bayley-III showed a 3% rate of severe deficits with 19% moderate disability and 33.5% of infants are at risk of deficits in this area. Van Handel et al. noted a few other studies that proposed that children with moderate encephalopathy have risk for developing hyperactivity[11]. Cognitive and language deficits have been associated with behavioural problems.

5.3.2.5.2 Comparison of baseline and reassessment

The adaptive behaviour components on the Bayley-III have an average scaled score of 7.5 at baseline for both groups with 3% of participants with severe dysfunction,

20.6% with moderate dysfunction and 26.5% at risk for delayed development in the group who received induced hypothermia at baseline. Again, the scores decreased on reassessment for this group with significant differences seen for Adaptive Behaviour: Communication (p=0.00), Adaptive Behaviour: Health and Safety (p=0.03), Adaptive Behaviour Leisure(p=0.02), Adaptive Behaviour Self-care (0.04) Adaptive Behaviour: Self direction (p= 0.01) and Adaptive Behaviour: Motor (p=0.00). It is clear in relation to the significant decrease in cognitive and language components, parents/caregivers were seeing a change in adaptive behaviour, specifically that related to occupational performance in self-care and leisure. The motor function could be related to fine motor changes (Table 4.10)[75]. This is related to the variability in the parents/caregivers' level of educational, nurturing, socioeconomic status and principle caregiver.

These findings are confirmed by the results for the group who did not receive induced hypothermia where 12% had moderate disability and 31% were at risk of developmental delay at baseline (Table 4.12). Although decreases in their scores were found at reassessment for cognitive and language scores, none of these changes were statistically significant. Confirming the relationship between the therapist assessed components and the adaptive behaviour components reported by parents.

When the groups were compared, there were no statistically significant differences between them at baseline. On reassessment, there was a significant difference between the groups for Adaptive Behaviour: Functional pre-academics (p=.0.04). More of those who received induced hypothermia presented with severe (8%) and moderate dysfunction (24%) compared to the 16% with moderate dysfunction for those who did not receive induced hypothermia. Less than 50% of participants in both groups were reported to have normal or above average development in terms of adaptive behaviour.

There are certain patterns of brain injury in neonatal encephalopathy that have been associated with cognitive and behavioural difficulties. The patterns include injury to the striatum and hippocampus, as these areas are associated with particular cognitive functions such as attention and memory. They have also been thought to be associated with schizophrenia, autism and ADHD[54]. Adaptive behaviour is the

component of greatest deficit out of all of the Bayley-III components in this study. This could be related to the pattern of brain injury but this information was not obtained in this study.

The remediation of adaptive behaviour especially for those related to occupational dysfunction such as leisure, self care and pre academics fall into the role of the occupational therapists. It is clear that this component needs to be addressed with these participants in specific intervention and home programmes.

5.3.2.5.3 Summary

In this study it was evident that there are limitations in the therapeutic interventions provided to infants with HIE. This study found that there were less than a quarter of infants who received therapeutic intervention in-hospital. This could be due to a number of factors i.e. limited referrals, limited awareness of the role of allied health professionals in the hospital and limited parent/caregiver knowledge of the role of allied health professionals. Intervention efforts are focused more on infants who have moderate to severe dysfunction particularly those with HIE III. More specific intensive transdisciplinary intervention is focused on these infants. All other infants are either monitored or provided with more general home programmes by the transdisciplinary team. As highlighted in this study, all infants presented with deterioration in their developmental deficits irrespective of the type of HIE, consequently a shift in the intervention planning would be beneficial.

5.4 HIE II and HIE III

On further analysis, it was evident that the HIE III group of children had a lower composite score in comparison to the HIE II group in terms of motor development. In this study only 9% of participants were diagnosed with HIE III and in this group there was only one participant who did not receive induced hypothermia, this infant was born at home. This child's motor abilities were severely limited (Scaled score of 1 for gross and fine motor development) which indicates that most of the participants were considered to develop typically in terms of their motor development. However, the HIE III group were significantly lower functioning when compared to the HIE II group, which is to be expected. Multiple research studies confirm this, in that it

shows that a large number of participants diagnosed with HIE II were at a higher functional level than children diagnosed with HIE III[6, 9, 15, 16, 43, 53, 59].

In terms of cognitive development, it was evident that the HIE III group of children had a lower composite score in comparison to the HIE II group. On initial assessment, the HIE II group had normal scaled scores for both groups, however the HIE III group presented with an at risk score (scaled score of seven) for the induced hypothermia group and severe deficit for the participant in the non-induced group. The HIE III participant who did not receive induced hypothermia had no changes in his cognitive, expressive language, fine motor or gross motor skills on reassessment, with only a minimal improvement in his receptive language.

Language development appears to be higher than average on initial assessment for both the HIE II and HIE III groups. On reassessment, the HIE II language components decreased for both the induced and non-induced hypothermia groups, however, scores remained within a normal range. For the HIE II group the participants who received induced hypothermia fell within a high average and the participant diagnosed with HIE III who did not receive induced hypothermia were at risk of developmental delay in terms of receptive language and had a severe deficit in expressive language.

A study by Marlow et al. (2005) discovered that parents/caregivers found that children with HIE III had a higher incidence of emotional problems and hyperactivity in comparison to children with HIE II. Furthermore, there were less pro-social behaviours. This had a significant impact on these children's everyday life and/or daily functioning. Pervasive behaviour disorders were also reported to be 8% in children with HIE II versus 23% in children with HIE III[101]. In this study, the HIE III group had 75% of participants with severe deficits in their socio emotional development whereas 20% of HIE II presented with severe deficits. In this study, the HIE II group had a composite score of 94 (normal) and the HIE III group had a composite score of 72.5 (moderate developmental deficits). The HIE III induced hypothermia group deteriorated in development for all areas (except fine motor). This is in keeping with literature that induced hypothermia may not have any effect on severe HIE[5].

5.5 Summary

The demographics factors in the study in terms of both groups that had received and had not received induced hypothermia are similar to those reported in developing and developed countries as supported by various other studies. There was a minimal difference in that the percentage of males with HIE was slightly higher than that found in the literature. There was a high prevalence of infants who were unexposed as well as HIV negative in this study, which correlated well with the PMTCT programme and reduced the risk of developmental delay in these infants. In contrast however, the rate of infants with seizures was high, which correlates with literature and increases the risk of developmental delay.

This study found that the majority of infant participants presented with HIE II. The rate of HIE III was found to be lower than a previous study done at CHBAH in 2013[68] prior to the initiation of induced hypothermia for these infants, indicating a decrease in the number of infants with HIE III. This is in keeping with the literature that induced hypothermia reduces the mortality as well as morbidity of infants with HIE. On closer analysis of the results however, it was evident that the level of disability was similar between the group that received induced hypothermia and the group that did not, which is not in keeping with literature.

Close to 75% of the infants in both the induced hypothermia and non-induced hypothermia groups presented with typical development on baseline assessment. This indicates that induced hypothermia is an effective modality as the infants with induced hypothermia are on par with their counterparts who did not receive induced hypothermia. There were 18.8% of infants at risk of developmental delay with only 9.6% presenting with moderate and severe deficits. This correlates with literature that reports the reduction in disability in infants with HIE that have received induced hypothermia.

The results indicated however that on reassessment the infant's developmental outcomes deteriorated significantly in all areas except for their gross motor skills. On reassessment 24.6% of infants were at risk of developmental delay with 11.6% presenting with moderate and severe deficits. This indicates that these infants will require more thorough assessment after the age of one.

This study has shown that assessing infants with HIE after the age of one is vital. The use of standardized assessments for the allied health professionals is recommended to ensure that developmental deficits in areas such as cognition and socio-emotional development are not over looked. As essential as early childhood intervention is, it is important to remember that deficits can appear at a later stage and must be identified for appropriate management.

5.6 Limitations of the Study

The limitations of this study include administration specific limitations as well as methodology limitations. The greatest limitation of this study was that the records and discharge summaries that were provided from the neonatal wards were not always adequate. The proposed plan was to obtain all the birth history and pregnancy information from the discharge summaries in the child's files, however, there was inconsistent information provided for the participants. Information that was not available had to be provided by the parents and caregivers, which is not always reliable due to language barriers, etc. This information was not included and did not affect analysis.

The setting where the children were assessed was not ideal. Originally, the plan was to assess the children in the therapy department to decrease distractions for optimal assessment, however, due to time constraints and lack of availability of alternative space the assessments had to be carried out in the HIE clinic itself which often had distractions.

Whilst performing the assessments, one of the limitations was the language barrier (minimal concern). This was particularly difficult for the parent/caregiver-evaluated components of the Bayley-III. The parents/caregivers required either translation or explanation of concepts that often did not have a direct translation into their home language inspite of the best efforts being made to translate these forms and describe this to the parents/caregivers.

The Bayley-III scale includes comprehensive information about early development and is administered in conjunction with a parent/caregiver questionnaire. Several publications suggested that the Bayley-III might underestimate neurodevelopmental

dysfunctions in infants[105, 107]. In a study done by Acton B et al in 2011 that compared Bayley-III to the Bayley scale of infant development – second edition (BSID –II) it was evident that the overall scores of children on the Bayley-III were 6.1 points higher than the scores on BSID-II with the most difference evident in the cognitive scores with a 10 point increase in the mean scores. Furthermore in a study by Aylward (2013) it was highlighted that developmental age norms needed to be analysed cautiously as there were issues with the test gradient as well as inaccuracies with developmental ages[107]. It is important to be aware of the limitations of attempting to understand something as complex and dynamic as development with one measurement tool alone [103, 104].

The participants in the non-induced hypothermia group had higher scores for development for all subtests on the Bayley-III compared to the participants who did receive induced hypothermia at baseline and reassessment. The results may have been affected as less than 50% of the participants who did not receive induced hypothermia returned for follow up assessment and results may reflect a biased reflection of the developmental levels for this group.

The small sample size in this study, especially for the number of participants who were diagnosed with HIE III, made it difficult to compare the HIE II and HIE III groups. Comparisons were therefore drawn between the groups that had received induced hypothermia versus those that had not. There were also 28% of children lost to follow up and most of these children were from the non-induced hypothermia group affecting the comparisons.

CHAPTER 6: CONCLUSION

This study provided insight into the specific developmental outcomes of infants with HIE at Chris Hani Baragwanath Academic Hospital. It furthermore provided an understanding of the differences in these infants that received whole-body induced hypothermia versus those that have not.

This was a quantitative study to determine the developmental outcomes of infants between the ages of five to 16 months with HIE and to compare the groups that have received induced hypothermia and those that had not. Forty-three infant participants were assessed using the Bayley-III at the HIE clinic at CHBAH. Thirty-nine of these infants were diagnosed with HIE II and attended the HIE clinic; these children were followed up regularly by the neonatologists and the allied health professionals team. All children received transdisciplinary early intervention and the parents were provided with the knowledge and skills to provide stimulation for their children at home. These infants were reassessed after three to nine months with the Bayley-III.

Demographic factors of the infant participants were analysed to understand the impact that these would have on development. It was evident that these participants were predominantly male, which correlated with the literature that males are more at risk of HIE than females. There are also certain factors that put an infant at higher risk of HIE and these include mode of delivery, assistance during delivery as well as low Apgar scores in the first five to ten minutes. One of the factors that put these infants at less risk was their HIV status, as they were predominantly negative or unexposed infants. To understand risk factors in more depth, an analysis of maternal health during pregnancy would be beneficial.

Literature reports a decrease in mortality and disability in infants with HIE who have received induced hypothermia. It was evident that the group that received induced hypothermia in this study presented with more of these risk factors than the group that did no receive induced hypothermia. In this study, 74.6% of infants presented with typical development for both the group that received induced hypothermia and the group that did not. On reassessment, however, it was evident that the development of these infants had deteriorated with a slight increase in the

proportion of infants presenting with moderate or severe developmental delay as well as a greater number being at risk of development delay. The only area of development that improved was that of gross motor skills.

On further analysis, language skills were significantly higher than all other areas of development overall. This variability in the overall group could be related to the type of brain injury as well as socioeconomic status as language and gross motor skills, which are more easily stimulated in a limited resource context. Other studies have also shown a decrease in developmental scores on the Bayley-III after nine months of age, as assessing aspects such as cognition in very young infants is difficult[70], thus the age at which the infants were assessed may also have affected the results.

In spite of both groups being on par developmentally on baseline assessment it was evident that the group that received induced hypothermia deteriorated in their scores to a risk level in cognition, expressive language and gross motor on reassessment. In spite of this, the percentage of participants with developmental delay was still lower than other studies. Due to limited resources and challenges at Chris Hani Baragwanath Academic Hospital (CHBAH), infants are often selected according to the first come principle than on severity of asphyxia indicating a possibility of more severe infants receiving induced hypothermia. The reasons for excluding certain asphyxiated infants and not providing them with induced hypothermia requires analysis. The majority of infants in this study are on par developmentally indicating that hypothermia is effective. Mild deficits placing infants at risk for developmental delay did become more evident at a later stage and are less severe than expected for infants with HIE.

The caregiver evaluated component of social-emotional development had lower scores than the therapist evaluated components of cognitive, language and motor skills. For infants who have more severe social-emotional problems, it is vital for more in-depth assessments to be performed to identify if they are at risk for autism to ensure early diagnosis of the condition, if present. Determining the most appropriate tool for this requires further investigation. There is also limited literature on the social-emotional development of children in South Africa and the impact that socioeconomic status has on this development, further research is needed.

Overall, the adaptive behaviour component of development indicated moderate deficits in this area with high variability in the results. This high variability can be related to the variability in the parents/caregivers level of education, nurturing, socioeconomic status and principle caregiver, which can skew the results. However this area of development is often overlooked in these infants but is an important consideration for understanding the long term functioning of these children. This is a vital role that occupational therapists have in relation to occupational dysfunction and needs to be thoroughly assessed and addressed.

In addition to a comparison between the group that received induced hypothermia and the group that did not, a comparison was made between the HIE II and HIE III groups. The HIE groups were analysed and it was evident that the HIE III group functioned at a significantly lower level in terms of their cognitive, language and motor skills which correlates with the literature. When comparing this group to a study done in 2013 at CHBAH, it was evident that the rate of HIE III had reduced, indicating a reduction in the number of infants with severe developmental deficits. In spite of receiving induced hypothermia, the HIE III infants presented with a deterioration in their development, which is in keeping with literature that induced hypothermia may not have an effect on severe HIE. However, the small sample size particularly for the HIE III group makes more specific and reliable comparisons difficult.

A more comprehensive understanding of the specific components of development in infants with HIE provides insight into the areas of development that require more focus in therapeutic intervention. Early transdisciplinary intervention is important and needs to consider that the development of infants with HIE deteriorates over time. It is therefore important that these infants receive therapeutic intervention after the age of one year old with more specific and standardized assessments at these later ages. This is to ensure that deficits in development are identified early to ensure more precise and effective therapeutic interventions and home programmes are provided.

6.1 RECOMMENDATIONS

Infants with HIE need to be followed up into their childhood (over the age of one year) in depth and this should be made a priority. By using standardised assessments i.e. Bayley-III, more specific and in-depth information can be obtained which will assist in the development of more focused, specifically structured and effective therapeutic interventions.

It is important for fellow health care professionals to document their history taking, assessment and treatment/management thoroughly. Using a standardised record keeping system or policy to ensure consistency would be most beneficial, this will also ensure that all information is available for all health care professionals to ensure the best practice.

This study should be replicated with a larger sample with a more precise methodology and rectifying issues i.e. recruitment and follow up. There is potential for a multicentre research to recruit larger numbers of participants. There is also a potential to investigate the effectiveness of therapeutic intervention provided to these infants.

REFERENCES

1. Pizur-Barnekow K, Darragh A and Johnston MV. “I cried because I didn’t know if I could take care of him”. Toward a taxonomy of interactive and critical health literacy as portrayed by caregivers of children with special health care needs. *Journal of Health Communication*. 2011; 16: 205-11.
2. McCary L and Roberts J. Early identification of autism in fragile X syndrome: a review. *Journal of Intellectual Disability Research*. 2013; 57: 803-14.
3. Sarnat HB and Sarnat MS. Neonatal encephalopathy following fetal distress. *Obstetrical & Gynecological Survey*. 1977; 32: 295.
4. Robertson CM and Perlman M. Follow-up of the term infant after hypoxic-ischemic encephalopathy. *Paediatrics & child health*. 2006; 11: 278.
5. Bayley N. *Bayley scales of infant and toddler development*. 2006.
6. Jacobs SE, Morley CJ, Inder TE, et al. Whole-body hypothermia for term and near-term newborns with hypoxic-ischemic encephalopathy: a randomized controlled trial. *Archives of pediatrics & adolescent medicine*. 2011; 165: 692-700.
7. Kurinczuk JJ, White-Koning M and Badawi N. Epidemiology of neonatal encephalopathy and hypoxic–ischaemic encephalopathy. *Early human development*. 2010; 86: 329-38.
8. Horn A, Swingler G, Myer L, et al. Defining hypoxic ischemic encephalopathy in newborn infants: benchmarking in a South African population. *Journal of Perinatal Medicine*. 2013; 41: 211– 7.
9. Laptook AR, Shankaran S, Ambalavanan N, et al. Outcome of term infants using apgar scores at 10 minutes following hypoxic-ischemic encephalopathy. *Pediatrics*. 2009; 124: 1619-26.
10. Horn AR. Early prediction of hypoxic ischaemic encephalopathy in newborn infants in a resource-limited setting. 2013.
11. Linley L, Thompson C, Greenfield D, Moller G and Fawcus S. Incidence, morbidity and mortality of hypoxic ischemic encephalopathy in the PMNS. *23rd Conference on Priorities in Perinatal Care in Southern Africa*. Limpopo, South Africa2004, p. 144-6.
12. Buchmann EJ and Velaphi SC. Confidential enquiries into hypoxic ischaemic encephalopathy. *Best Practice & Research Clinical Obstetrics & Gynaecology*. 2009; 23: 357-68.
13. Jacobs S, Berg M, Hunt R, Tarnow-Mordi W, Inder T and Davis P. Cooling for newborns with hypoxic ischaemic en-cephalopathy. *status and date: Edited (no change to conclusions), published in*. 2013.
14. Fatemi A, Wilson M and Johnston M. Hypoxic Ischaemic Encephalopathy in the term infant. *Clinical Perinatology*. 2009; 36: 835-58.
15. Shankaran S, Pappas A, Laptook A, et al. Outcomes of safety and effectiveness in amulticentre Randomized, Controlled Trial of whole body hypothermia for neonatal Hypoxic Ischemic Encephalopathy. *Official Journal of the American Academy of Pediatrics*. 2008; 122: e791-8.
16. Zanelli S, Naylor M, Dobbins N, et al. Implementation of a ‘Hypothermia for HIE’program: 2-year experience in a single NICU. *Journal of Perinatology*. 2008; 28: 171-5.
17. Olsen SL, DeJonge M, Kline A, et al. Optimizing therapeutic hypothermia for neonatal encephalopathy. *Pediatrics*. 2013; 131: e591-e603.
18. Halloran D, McClure E, Chakraborty H, Chomba E, Wright L and Carlo W. Birth asphyxia survivors in developing countries. *Journal of Perinatology*. 2009; 29: 243–9.
19. Hamilton S. Screening for developmental delay: Reliable, easy-to-use tools. *Journal of Family Practice*. 2006; 55: 415.

20. Case-Smith J and Clifford O'Brien J. *Occupational Therapy for Children*. Philadelphia: Elsevier Health Sciences, 2013.
21. Valvano J and Rapport M. Activity- focused motor interventions for infants and young children with neurological conditions. *Infants and young children*. 2006; 19.
22. Bartlett DJ. Comparison of 15-month motor and 18-month neurological outcomes of term infants with and without motor delays at 10-months-of-age. *Physical & occupational therapy in pediatrics*. 2000; 19: 61-72.
23. De Silva R. Hypoxic ischaemic encephalopathy. *6th Congress of the Paediatric Association of South Asian Countries and 12th Annual Scientific Congress of the Sri Lanka College of Paediatricians* 2009, p. 40.
24. Hanna K and Rodger S. Towards family-centred practice in paediatric occupational therapy: A review of the literature on parent–therapist collaboration. *Australian Occupational Therapy Journal*. 2002; 49: 14-24.
25. Jowitt M. Hypoxic ischaemic encephalopathy. *Association for Improvements in the Maternity Services Journal*. 2010; 22: 13-5.
26. Kali GTJ, Martinez-Biarge M, Van Zyl J, Smith J and Rutherford M. Management of therapeutic hypothermia for neonatal hypoxic ischaemic encephalopathy in a tertiary centre in South Africa. *Archives of Disease in Childhood-Fetal and Neonatal Edition*. 2015: fetalneonatal-2015-308398.
27. Mackay-Jones K, Molyneux E, Phillips B and Wieteska S. *The Burned or Scalded Child. In: Advanced Paediatric Life Support – The Practical Approach*. 4th ed. Hoboken: BMJ Books, 2005.
28. Thornton C, Rousset CI, Kichev A, et al. Molecular mechanisms of neonatal brain injury. *Neurology research international*. 2012; 2012.
29. Herrera-Marschitz M, Neira-Pena T, Rojas-Mancilla E, et al. Perinatal asphyxia: CNS development and deficits with delayed onset. *Frontiers in neuroscience*. 2014; 8.
30. Jacobs SE, Hunt R, Tarnow-Mordi WO, Inder TE and Davis PG. Cochrane Review: Cooling for newborns with hypoxic ischaemic encephalopathy. *Evidence-Based Child Health: A Cochrane Review Journal*. 2008; 3: 1049-115.
31. Mackay-Jones K, Molyneux E, Phillips B and Weeteska S. Advanced Pediatric Life Support-The Practical Approach. 2nd ed. London: Advanced Life Support Group, 1997.
32. Perlman JM. Summary proceedings from the neurology group on hypoxic-ischemic encephalopathy. *Pediatrics*. 2006; 117: S28-S33.
33. Nagdyman N, Kömen W, Ko H-K, Müller C and Obladen M. Early biochemical indicators of hypoxic-ischemic encephalopathy after birth asphyxia. *Pediatric research*. 2001; 49: 502-6.
34. de Vries LS and Groenendaal F. Patterns of neonatal hypoxic–ischaemic brain injury. *Neuroradiology*. 2010; 52: 555-66.
35. Horn A. Early prediction of hypoxic ischemic encephalopathy. *23rd Conference on Priorities in Perinatal Care in Southern Africa;*. Cape Town, South Africa.2004, p. 142-4.
36. Robertson NJ, Nakakeeto M, Hagmann C, et al. Therapeutic hypothermia for birth asphyxia in low-resource settings: a pilot randomised controlled trial. *The Lancet*. 2008; 372: 801-3.
37. Palsdottir K, Dagbjartsson A, Thorkelsson T and Hardardottir H. [Birth asphyxia and hypoxic ischemic encephalopathy, incidence and obstetric risk factors]. *Laeknabladid*. 2007; 93: 595-601.
38. Badawi N, Kurinczuk J, Keogh J, et al. Intrapartum risk factors for newborn encephalopathy: the Western Australian case-control study. *British Medical Journal*. 1998; 317: 1554-8.
39. Fawcus S and Van Zyl H. Obstetric risk factors for neonatal encephalopathy. *23rd Conference on Priorities in Perinatal Care in Southern Africa*. Cape Town2004, p. 142-4.

40. Badawi N, Kurinczuk J, Keogh J, et al. Antepartum risk factors for newborn encephalopathy: the Western Australian case-control study. *British Medical Journal*. 1998; 317: 1549-53.
41. Hallberg B. *Hypoxic ischemic encephalopathy: Diagnosis, hypothermia treatment and outcome*. Institutionen för klinisk vetenskap/Department of Clinical Sciences, 2010.
42. Thoresen M and Whitelaw A. Therapeutic hypothermia for hypoxic–ischaemic encephalopathy in the newborn infant: review. *Current opinion in neurology*. 2005; 18: 111-6.
43. Sukha N. The developmental motor outcomes of infants with hypoxic ischaemic encephalopathy II and III between the ages of 12-14 months at Chris Hani Baragwanath academic hospital. *Occupational Therapy*. University of the Witwatersrand, 2014.
44. Simbruner G, Mittal RA, Rohlmann F and Muche R. Systemic hypothermia after neonatal encephalopathy: outcomes of neo. nEURO. network RCT. *Pediatrics*. 2010; 126: e771-e8.
45. Kwon JM, Guillet R, Shankaran S, et al. Clinical seizures in neonatal hypoxic-ischemic encephalopathy have no independent impact on neurodevelopmental outcome: secondary analyses of data from the neonatal research network hypothermia trial. *Journal of child neurology*. 2010: 0883073810380915.
46. Ilah B, Aminu M, Musa A, Adelakun M, Adeniji A and Kolawole T. Prevalence and Risk Factors for Perinatal Asphyxia as Seen at a Specialist Hospital in Gusau, Nigeria. *Sub-Saharan African Journal of Medicine*. 2015; 2: 64.
47. Glass HC, Glidden D, Jeremy RJ, Barkovich AJ, Ferriero DM and Miller SP. Clinical neonatal seizures are independently associated with outcome in infants at risk for hypoxic-ischemic brain injury. *The Journal of pediatrics*. 2009; 155: 318-23.
48. Thompson C, Puterman A, Linley L, et al. The value of a scoring system for hypoxic ischaemic encephalopathy for predicting neurodevelopmental outcome. *Acta Paediatrica*. 1997; 86: 757-61.
49. Velaphi S and Pattinson R. Avoidable factors and causes of neonatal deaths from perinatal asphyxia-hypoxia in South Africa: national perinatal survey. *Annals of Tropical Paediatrics*. 2007; 27: 99–106.
50. Pattinson R. Saving babies 2003-2005: Fifth perinatal care survey of South Africa. *Pretoria: University of Pretoria, Medical Research Council of South Africa, Centres for Disease Control*. 2007.
51. Ellis M, Shresthra L, Shresthra P, Manandhar D, Bolam A and De L Costello A. Clinical predictors of outcome following mild and moderate neonatal encephalopathy in term newborns in Kathmandu, Nepal. *Acta Paediatrics*. 2001; 90: 316- 22.
52. Murray DM, Bala P, O'CONNOR CM, Ryan CA, Connolly S and Boylan GB. The predictive value of early neurological examination in neonatal hypoxic–ischaemic encephalopathy and neurodevelopmental outcome at 24 months. *Developmental Medicine & Child Neurology*. 2010; 52: e55-e9.
53. Garbutt A and Trotman H. Outcome of neonates with hypoxic ischaemic encephalopathy admitted to the neonatal unit of the university Hospital of the West Indies. *Annals of Tropical Pediatrics*. 2009; 29: 263-9.
54. Van Handel M, Swaab H, De Vries L and Jongmans M. Long- term cognitive and behavioural consequences of neonatal encephalopathy following perinatal asphyxia:a review. *European Journal of Pediatrics*. 2007; 166: 645-54.
55. De Vries LS and Jongmans MJ. Long-term outcome after neonatal hypoxic-ischaemic encephalopathy. *Archives of Disease in Childhood-Fetal and Neonatal Edition*. 2010; 95: F220-F4.
56. Wintermark P. Current controversies in newer therapies to treat birth asphyxia. *International journal of pediatrics*. 2011; 2011.
57. Gluckman PD, Wyatt JS, Azzopardi D, et al. Selective head cooling with mild systemic hypothermia after neonatal encephalopathy: multicentre randomised trial. *The Lancet*. 2005; 365: 663-70.

58. Shankaran S, Laptook AR, Ehrenkranz RA, et al. Whole-body hypothermia for neonates with hypoxic–ischemic encephalopathy. *New England Journal of Medicine*. 2005; 353: 1574-84.
59. Azzopardi DV, Strohm B, Edwards AD, et al. Moderate hypothermia to treat perinatal asphyxial encephalopathy. *New England Journal of Medicine*. 2009; 361: 1349-58.
60. Zhou W-h, Cheng G-q, Shao X-m, et al. Selective head cooling with mild systemic hypothermia after neonatal hypoxic-ischemic encephalopathy: a multicenter randomized controlled trial in China. *The Journal of pediatrics*. 2010; 157: 367-72. e3.
61. Hindley C. The Griffiths Scale of Infant Development: Scores and predictions from 3 to 18 months. *Journal of Child Psychology and Psychiatry*. 1960; 1: 99-112.
62. Edwards AD, Brocklehurst P, Gunn AJ, et al. Neurological outcomes at 18 months of age after moderate hypothermia for perinatal hypoxic ischaemic encephalopathy: synthesis and meta-analysis of trial data. *Bmj*. 2010; 340.
63. Hankins GD and Speer M. Defining the pathogenesis and pathophysiology of neonatal encephalopathy and cerebral palsy. *Obstetrics & Gynecology*. 2003; 102: 628-36.
64. Rutherford M, Ramenghi LA, Edwards AD, et al. Assessment of brain tissue injury after moderate hypothermia in neonates with hypoxic–ischaemic encephalopathy: a nested substudy of a randomised controlled trial. *The Lancet Neurology*. 2010; 9: 39-45.
65. Shah PS, Ohlsson A and Perlman M. Hypothermia to treat neonatal hypoxic ischemic encephalopathy: systematic review. *Archives of pediatrics & adolescent medicine*. 2007; 161: 951-8.
66. Eicher DJ, Wagner CL, Katikaneni LP, et al. Moderate hypothermia in neonatal encephalopathy: efficacy outcomes. *Pediatric neurology*. 2005; 32: 11-7.
67. Lindström K, Hallberg B, Blennow M, Wolff K, Fernell E and Westgren M. Moderate neonatal encephalopathy: Pre-and perinatal risk factors and long-term outcome. *Acta obstetricia et gynecologica Scandinavica*. 2008; 87: 503-9.
68. Johnson S, Moore T and Marlow N. Using the Bayley-III to assess neurodevelopmental delay: which cut-off should be used? *Pediatric research*. 2014; 75: 670-4.
69. Aina O and Morakinyo O. Normative data on mental and motor development in Nigerian children. *West African journal of medicine*. 2005; 24: 151-6.
70. Rademeyer V and Jacklin L. 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*. 2013; 7: 54-9.
71. Luiz DM, Foxcroft CD and Povey J-L. The Griffiths scales of mental development: A factorial validity study. *South African Journal of Psychology*. 2006; 36: p. 192-214.
72. Cockcroft K, Amod Z and Soellaart B. Level of maternal education and performance of Black, South African infants on the 1996 Griffiths Mental Development Scale. *African Journal of Psychiatry*. 2008; 11: 44-50.
73. Beail N. A comparative study of profoundly multiply handicapped children's scores on the Bayley and the Griffiths developmental scales. *Child: Care, health and development*. 1985.
74. McLean M, McCormick K and Baird SM. Concurrent validity of the Griffiths' Mental Development Scales with a population of children under 24 months. *Journal of Early Intervention*. 1991; 15: 338-44.
75. Carson DK, Klee T, Perry CK, Muskina G and Donaghy T. Comparisons of children with delayed and normal language at 24 months of age on measures of behavioral difficulties, social and cognitive development. *Infant mental health journal*. 1998; 19: 59-75.
76. Stedman TL. Stedman's medical dictionary. 1990.
77. Kaplan H and Kaplan SB. Sadock's. Synopsis of psychiatry: behavioral sciences/clinical psychiatry. *Trans Pourafkari N Tehran: Shahrab Pub*. 2007: 534-88.
78. Heineman K, Middelburg K and Hadders-Algra M. Development of adaptive motor behaviour in typically developing infants. *Acta Paediatrica*. 2010; 99: 618-24.
79. Bly L. *Components of typical and atypical motor development*. Neuro-Developmental Treatment Association, Incorporated, 2011.

80. Albers CA and Grieve AJ. Test review: Bayley Scales of Infant and Toddler Development-Third Edition. *Journal of Psychoeducational Assessment,* . 2006; 25: 180-1.
81. Chalak LF, DuPont TL, Sánchez PJ, et al. Neurodevelopmental outcomes after hypothermia therapy in the era of Bayley-III. *Journal of Perinatology*. 2014; 34: 629-33.
82. Rodger S, Brown G and Brown A. Profile of paediatric occupational therapy practice in Australia. *Australian Occupational Therapy Journal*. 2005; 52: 153-80.
83. Colver A. What are we trying to do for disabled children? *Current Paediatrics*. 2006; 16: 501-5.
84. Mahoney G RC, Perales F. Early Motor Intervention: The Need for New Treatment Paradigms. *Infants and young Children*. 2004; 17.
85. Veličković TD and Perat MV. Basic principles of the neurodevelopmental treatment. 2005.
86. Graham JV, Eustace C, Brock K, Swain E and Irwin-Carruthers S. The Bobath concept in contemporary clinical practice. *Topics in stroke rehabilitation*. 2009; 16: 57.
87. Mayston M. Bobath Concept: Bobath@ 50: mid-life crisis—What of the future? *Physiotherapy Research International*. 2008; 13: 131-6.
88. Joolay Y, Harrison MC and Horn AR. Therapeutic hypothermia and hypoxic ischemic encephalopathy: opinion and practice of pediatricians in South Africa. 2012.
89. Akar M, Aydemir O, Oguz S, et al. Whole body cooling method with hypothermia applied hypoxic-ischemic encephalopathy evaluation of newborns. *Turkish Archives of Pediatrics* 2011; 46.
90. Thalheimer W and Cook S. How to calculate effect sizes from published research: A simplified methodology. *Work-Learning Research*. 2002: 1-9.
91. National Department of Health SA. CLINICAL GUIDELINES: PMTCT (Prevention of Mother-to-Child Transmission). Pretoria: South African National AIDS Council, 2010.
92. Bruckmann EK and Velaphi S. Intrapartum asphyxia and hypoxic ischaemic encephalopathy in a public hospital: Incidence and predictors of poor outcome. *SAMJ: South African Medical Journal*. 2015; 105: 298-303.
93. Padayachee N. outcomes of neonates with perinatal asphyxia at Charlotte Maxeke Johannesburg academic hospital (CM JAH) from 2007-2011. 2015.
94. Bari M, Ullah M and Khatun M. Morbidity and mortality of low birth weight baby. *TAJ: Journal of Teachers Association*. 2008; 21: 35-9.
95. Lee AC, Mullany LC, Tielsch JM, et al. Risk factors for neonatal mortality due to birth asphyxia in southern Nepal: a prospective, community-based cohort study. *Pediatrics*. 2008; 121: e1381-e90.
96. Cowan F, Rutherford M, Groenendaal F, et al. Origin and timing of brain lesions in term infants with neonatal encephalopathy. *The Lancet*. 2003; 361: 736-42.
97. Shankaran S, Barnes PD, Hintz SR, et al. Brain injury following trial of hypothermia for neonatal hypoxic–ischaemic encephalopathy. *Archives of Disease in Childhood-Fetal and Neonatal Edition*. 2012; 97: F398-F404.
98. De Knijf A, Delport S and Pattinson R. Confidential Enquiries into hypoxic ischemic encephalopathy as a marker for assessing the quality of care of women in labour. *30th Conference on Priorities in Perinatal Care in Southern Africa*. Limpopo, South Africa2011, p. .224.
99. Cooper P. Analysis of term asphyxiated infants at Bara hospital. *11th Conference on Priorities in Perinatal Care in South Africa*. Department of Pediatrics, University of the Witwatersrand1992.
100. The South African Social Service Agency (SASSA). Social Grants. Pretoria2015.
101. Marlow N, Rose A, Rands C and Draper E. Neuropsychological and educational problems at school age associated with neonatal encephalopathy. *Archives of Disease in Childhood-Fetal and Neonatal Edition*. 2005; 90: F380-F7.
102. Gonzalez F and Miller S. Does perinatal asphyxia impair cognitive function without cerebral palsy? *Archives of Disease in Childhood-Fetal and Neonatal Edition*. 2006; 91: F454-F9.

103. Acton BV, Biggs WS, Creighton DE, et al. Overestimating neurodevelopment using the Bayley-III after early complex cardiac surgery. *Pediatrics*. 2011; 128: e794-e800.
104. Lowe JR, Erickson SJ, Schrader R and Duncan AF. Comparison of the Bayley II Mental Developmental Index and the Bayley III Cognitive Scale: are we measuring the same thing? *Acta paediatrica*. 2012; 101: e55-e8.
105. Savchev S, Sanz-Cortes M, Cruz-Martinez R, et al. Neurodevelopmental outcome of full-term small-for-gestational-age infants with normal placental function. *Ultrasound in Obstetrics & Gynecology*. 2013; 42: 201-6.
106. Badawi N, Dixon G, Felix JF, et al. Autism following a history of newborn encephalopathy: more than a coincidence? *Developmental Medicine & Child Neurology*. 2006; 48: 85-9.
107. Aylward GP. *Practitioner's guide to developmental and psychological testing*. Springer Science & Business Media, 2013.

APPENDICES

APPENDIX A:

Sarnat clinical staging of hypoxic ischaemic encephalopathy (HIE):

(Sarnat HB, Sarnat MS. Neonatal encephalopathy following fetal distress, a clinical and electroencephalographic study. Archives of Neurology. 1976; 33:701).

Variable	**Level of consciousness**		
	Alert/hyperalert	**Lethargy**	**Coma**
	Stage I (HIE I)	**Stage II (HIE II)**	**Stage III (HIE III)**
Muscle tone	Normal	Hypotonia	Flaccidity
Seizures	Absent	Focal or multifocal	Decerebration/ generalized
Complex reflexes:			
Suck	Active	Weak	Absent
Moro	Exaggerated	Incomplete	Absent
Grasp	Normal/exaggerated	Weak	Absent
Tonic Neck	Slight	Strong	Absent
Autonomic functions:			
Pupils	Mydriasis	Miosis	Variable, often unequal poor light reflex, fixed dilated
Heart rate	Tachycardia	Bradycardia	Variable
Level of consciousness	Hyperalert	Lethargic or obtunded	Stupor or coma
Activity	Normal	Decreased	Absent
Neuromuscular control:			
Muscle tone	Normal	Mild hypotonia	Flaccid
Posture	Mild distal flexion	Strong distal flexion	Intermittent decerebration
Stretch reflexes	Overactive	Overactive	Decreased or absent

APPENDIX B:

DEMOGRAPHIC QUESTIONNAIRE

PERSONAL INFORMATION

To be kept separate by the researcher

CODE _____

Name: _____

Hospital number: _____

Date of birth:_____

Address: _____

_____

_____

Contact number: _____

Hospital classification:_____

Induced whole-body hypothermia: YES/NO

DEMOGRAPHIC QUESTIONNAIRE:

CODE _____

1. **Birth History:**

Birth History	
Place:	
NVD/C-section:	
Forceps/Vacuum:	
Gestation:	
Birth wt:	
Apgars:	
RVD status:	
Additional history:	

Period of stay in maternity ward (NICU, TICU and maternity with specific time frames):

_____

2. **Medical history:**

Significant medical events

_____

_____

Admissions and reasons for these

_____

_____

Co-morbidities

_____

_____

3. Residential facilities:

In what type of housing do you live? _____

Do you have access to water, electricity and toilet facilities:_____

4. Social support:

Who do you live with?

_____

Who assists you with your child if need be?

---

5. Interests:

What types of toys is your child interested in?

APPENDIX C:

Bayley Scales of Infant and Toddler Development 3rd Edition (Bayley–III)[5, 80]

Bayley–III measures adaptive behavior, cognitive, language, motor and socio-emotional areas of development.

Adaptive Behavior:

- Communication
- Community use
- Functional pre-academics
- Home Living
- Health and Safety
- Leisure
- Self-care
- Self-direction
- Social
- Motor

Cognitive:

- Sensorimotor development
- Exploration and manipulation
- Object relatedness
- Concept formation
- Memory
- Habituation
- Visual acuity
- Visual preference
- Object permanence
- Plus other aspects of cognitive processing

Items measure age-appropriate skills including:

- Counting (with one-to-one correspondence and cardinality)
- Visual and tactile exploration
- Object assembly
- Puzzle board completion
- Matching colors
- Comparing masses

- Representational and pretend play
- Discriminating patterns

Language:

Expressive communication

Assesses preverbal communications such as:

- Babbling
- Gesturing
- Joint referencing
- Turn taking
- Vocabulary development such as naming objects, pictures and actions
- Morpho-syntactic development such as use of two-word utterances and use of plurals and verb tense.

Receptive communication

Assesses preverbal behaviors and vocabulary development such as:

- The ability to identify objects and pictures that are referenced
- Vocabulary related to morphological development such as pronouns and prepositions
- Understanding of morphological markers such as plurals and tense markings

Motor:

Fine motor

Fine motor skills associated with:

- Prehension
- Perceptual – motor integration
- Motor planning
- Motor speed

Items measure age-appropriate skills including:

- Visual tracking
- Reaching
- Object manipulation
- Grasping
- Children's quality of movement
- Functional hand skills
- Response to tactile information (sensory integration)

Gross motor

Items assess:

- Static positioning (e.g. head control, sitting, standing)
- Dynamic movement including locomotion (crawling, walking, running, jumping, walking up and down stairs)
- Quality of movement (coordination when standing up, walking, kicking)
- Balance
- Motor planning
- Perceptual – motor integration (e.g. imitating postures)

Socio-emotional

- Determines the mastery of early capacities of social-emotional growth
- Monitors healthy social and emotional functioning
- Monitors progress in early intervention programs
- Detects deficits or problems with developmental social-emotional capacitities.
- 0-3 months: Exhibits growing, self-regulation, and interest n the world
- 4-5 months: Engages in relationships
- 6-9 months: Uses emotions in an interactive, purposeful manner
- 10-14 months: Uses a series of interactive, emotional signals or gestures to communicate
- 15-18 months: Uses a series of interactive, emotional signals or gestures to solve problems
- 19-30 months: Uses ideas to convey feelings, wishes or intentions

31-42 months: Creates logical bridges between emotions and ideas.

APPENDIX D:

R14/49 Ms Bianca Pereria

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M140489

NAME: (Principal Investigator)	Ms Bianca Pereria
DEPARTMENT:	Occupational Therapy Chris Hani Baragwanath Academic Hospital
PROJECT TITLE:	Developmental Outcomes for Infants with Hypoxic Ischaemic Encephalopathy (HIE) that have and have not Undergone Whole-Body Hypothermia
DATE CONSIDERED:	25/04/2014
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Denise Franzen and Firdose Nakwa
APPROVED BY:	Professor P Cleaton-Jones, Co-Chairperson, HREC (Medical)
DATE OF APPROVAL:	09/06/2014

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Secretary in Room 10004, 10th floor, Senate House, University.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report.**

Principal Investigator Signature Date 09/06/2014

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

APPENDIX E: Permission from CEO/Management at CHBAH

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

MEDICAL ADVISORY COMMITTEE
CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL

PERMISSION TO CONDUCT RESEARCH

Date: 08 July 2014

TITLE OF PROJECT: The developmental outcomes for infants with hypoxic ischaemic encephalopathy (HIE) that have and have not undergone whole-body hypothermia

UNIVERSITY: Witwatersrand

Principal Investigator: B Pereira

Department: Occupational Therapy

Supervisor (If relevant): D Franzen/F Nakwa

Permission Head Department (where research conducted): Yes

Date of start of proposed study: July 2014
Date of completion of data collection: December 2016

he Medical Advisory Committee recommends that the said research be conducted at Chris Hani Baragwanath Hospital. The CEO /management of Chris Hani Baragwanath Hospital is accordingly informed and the study is subject to:-

- Permission having been granted by the Committee for Research on Human Subjects of the University of the Witwatersrand.
- the Hospital will not incur extra costs as a result of the research being conducted on its patients within the hospital
- the MAC will be informed of any serious adverse events as soon as they occur
- permission is granted for the duration of the Ethics Committee approval.

.....
Recommended
(On behalf of the MAC)
Date: 08 July 2014

.....
Approved/Not Approved
Hospital Management
Date: 08/07/14

APPENDIX F: Permission from Occupational Therapy at CHBAH

PERMISSION LETTER FOR A STUDY ON THE DEVELOPMENTAL OUTCOMES FOR INFANTS WITH HYPOXIC ISCHAEMIC ENCEPHALOPATHY (HIE) THAT HAVE AND HAVE NOT UNDERGONE WHOLE-BODY HYPOTHERMIA

GAUTENG HEALTH

To: The Head of Department of Occupational Therapy at Chris Hani Baragwanath Academic Hospital
Post Office Bertsham 2013
Tel. (011) 933-8000
Fax (011) 938-1005

Researcher's name: Bianca Pereira

Supervisor's name: Denise Franzsen and Dr. Firdose Nakwa

University of the Witwatersrand Occupational therapy department.

The purpose of this study is to investigate the difference in the developmental outcomes for infants who have been in a whole-body hypothermia protocol versus those who have not. Adaptive behaviour, cognition, language, motor and socio-emotional areas of development will be assessed in an experimental and control group over a period of eight months. Both groups will receive transdisciplinary neurodevelopmental therapy at Chris Hani Baragwanath Academic hospital.

The objectives of the study are:

- To describe the different areas of developmental outcomes present in infants with HIE.
- To compare the developmental outcomes of infants with HIE at Chris Hani Baragwanath Academic hospital who have received induced whole body hypothermia at birth versus those who have not after attending an early intervention transdisciplinary NDT program for eight months.

In order for this study to be possible permission will be required to use the infants with hypoxic ischemic encephalopathy attending the Chris Hani Baragwanath Academic hospital's HIE and Neonatal Follow up (NNFU) clinics in the study. These infants will be required to

attend transdisciplinary neurodevelopmental therapy monthly for eight months for evaluations and treatment.

Please complete the attached letter should permission be granted.

Permission letter for the study on the developmental outcomes for infants with Hypoxic Ischaemic Encephalopathy (HIE) that have and have not undergone whole-body hypothermia.

Date:

Bianca Pereira

Occupational Therapy Department

University of the Witwatersrand

Dear Ms. Bianca Pereira

Thank you for your request to recruit participants from Chris Hani Baragwanath Academic Hospital for the above named research.

I have read and understood the Explanatory document regarding the research and hereby give permission for this research and hereby give permission for this research to be conducted.

Stipulations/clauses about recruitment of human participants:

Yours Sincerely,

Signature

Lynn Soulsby

Full name

AD -OT.

Designation

APPENDIX G: Permission from Neonatology at CHBAH

PERMISSION LETTER FOR A STUDY ON THE DEVELOPMENTAL OUTCOMES FOR INFANTS WITH HYPOXIC ISCHAEMIC ENCEPHALOPATHY (HIE) THAT HAVE AND HAVE NOT UNDERGONE WHOLE-BODY HYPOTHERMIA

GAUTENG HEALTH

To: The Head of the Neonatology Unit at Chris Hani Baragwanath Academic Hospital
Post Office Bertsham 2013
Tel. (011) 933-8000
Fax (011) 938-1005

Researcher's name: Bianca Pereira

Supervisor's name: Denise Franzsen and Dr. Firdose Nakwa

University of the Witwatersrand Occupational therapy department.

The purpose of this study is to investigate the difference in the developmental outcomes for infants who have been in a whole-body hypothermia protocol versus those who have not. Adaptive behaviour, cognition, language, motor and socio-emotional areas of development will be assessed in an experimental and control group over a period of eight months. Both groups will receive transdisciplinary neurodevelopmental therapy at Chris Hani Baragwanath Academic hospital.

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- To describe the different areas of developmental outcomes present in infants with HIE.
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In order for this study to be possible permission will be required to use the infants with hypoxic ischemic encephalopathy attending the Chris Hani Baragwanath Academic hospital's HIE and Neonatal Follow up (NNFU) clinics in the study. These infants will be required to

attend transdisciplinary neurodevelopmental therapy monthly for eight months for evaluations and treatment.

Please complete the attached letter should permission be granted.

Permission letter for the study on the developmental outcomes for infants with Hypoxic Ischaemic Encephalopathy (HIE) that have and have not undergone whole-body hypothermia.

Date:

Bianca Pereira

Occupational Therapy Department

University of the Witwatersrand

Dear Ms. Bianca Pereira

Thank you for your request to recruit participants from Chris Hani Baragwanath Academic Hospital for the above named research.

I have read and understood the Explanatory document regarding the research and hereby give permission for this research and hereby give permission for this research to be conducted.

Stipulations/clauses about recruitment of human participants:

Yours Sincerely,



Signature

Sithembiso Velaphi

Full name

Head of Department

Designation

APPENDIX H: Parent Consent Form

The developmental outcomes for infants with hypoxic ischaemic encephalopathy (HIE) that have and have not received whole-body induced hypothermia.

INFORMED CONSENT FORM

I,_____ _, confirm that I have received, read and understood the written information regarding the study.

I understand that at any stage, I may take myself out of the study. I understand that if I decide not to take part, or I change my mind, there will be no consequences for me. I have been given the opportunity to ask questions and am satisfied that they have been answered satisfactorily.

I agree that I will volunteer to take part in this study.

Signature: _____

Name: _____

APPENDIX I: Information Document

INFORMATION DOCUMENT

Study Title: The developmental outcomes for infants with hypoxic ischaemic encephalopathy (HIE) that have and have not received whole-body induced hypothermia.

Hello,

I, Bianca Pereira am doing research on hypoxic ischemic encephalopathy (HIE). Research is just part of learning the answer to a question. I want to learn if therapy can be used to help infants with this condition. I am inviting you and your baby to take part in this research study as your baby has been diagnosed with hypoxic ischaemic encephalopathy (HIE).

What is involved in the study:

I am asking that you attend the paediatric neurological rehabilitation clinic every month for eight months. Your baby will be assessed by me at your initial assessment. You will be interviewed to obtain important information that will help us design a therapy programme for your child. I will assess the way that your child moves, communicate, thinks and behaves. This assessment will take approximately 45 to 60 minutes.

Once your baby has been assessed, you will be booked for therapy. The therapy you will receive will include working on your child's head, trunk and limb control; hand function; visual abilities; communication; participation in play and in activities of daily living i.e. washing, dressing, eating. The therapy for your baby will be carried out by a therapy team of an occupational therapist, physiotherapist and speech therapist. After a few months of therapy you will be reassessed using the same tests you did at the start of the research to see what change there has been.

Participation is voluntary; refusal to participate will involved no penalty or loss of benefits to you. You may discontinue participation at any time without any penalty or loss of benefits. Efforts will be made to keep personal information confidential and only codes and not your name will be used on all questionnaires. Absolute confidentiality cannot be guaranteed but all identifying data will be kept separate by the researcher in a safe place. Personal information may be disclosed if required by law. All data will be stored for six years as required by HPCSA standards and organizations that may inspect and/or copy the research records for quality assurance and data analysis include groups such as the Research Ethics Committee.

The results of the research will be available on request.

Please contact me for any further information or if you have any concerns regarding your therapy process at 082 510 6151. To report any complaints or problems with ethics please feel free to contact: Professor Cleaton Jones, the chairperson of the Human Research Ethics Committee at the University of the Witwatersrand on 011 717 1234

Bianca Pereira
BSc (OT)