THE TRAJECTORY OF GENERAL MOVEMENTS FROM BIRTH UNTIL 12-14 WEEKS CORRECTED AGE IN PRETERM INFANTS BORN BEFORE 33 WEEKS' GESTATION AND WEIGHING LESS THAN 1500g: A DESCRIPTIVE STUDY

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Thesis presented in partial fulfilment of the requirements for the degree of Masters of Physiotherapy in the Faculty of Medicine and Health Sciences at Stellenbosch University

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APRIL 2019

DECLARATION

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ABSTRACT

BACKGROUND

Preterm infants remains a high risk group for developing neurological deficits such as cerebral palsy (CP). Early identification is important for timely intervention. Tygerberg Children's Hospital (TCH) is a public hospital with limited resources. It is the biggest neonatal service in the Western Cape. Clinicians depend on a reliable screening method to identify high risk infants in order to allocate resources effectively. Prof. Heinz Prechtl and his co-workers introduced a quick, inexpensive, non-invasive method with high predictive validity for the early detection of those premature infants at risk for later developmental deficits. This method, called general movements (GMs), is based on the assessment of spontaneous movement patterns in young infants. There is limited information available describing the trajectory of GMs in high risk premature infants.

OBJECTIVE

To describe the trajectories of GMs from birth till 12-14 weeks corrected age and determine the association of known perinatal risk factors on GM trajectories in very low birth weight and extremely low birth weight preterm infants admitted to the neonatal intensive care unit of TCH, Cape Town, South Africa.

METHODOLOGY

A longitudinal, prospective cohort study with repeated measures was conducted using Prechtl's method of the qualitative assessment of GMs at the following four key time periods: birth to 33 weeks postmenstrual age (PMA), 34-37 weeks PMA, term age and 12-14 weeks corrected age. Detailed perinatal data of infants were collected. Results were analysed using STATA version 14, IBM SPSS and a logistic regression model to determine the association between perinatal factors and GM outcome.

RESULTS

The study sample consisted of 119 infants with a mean birth weight of 1048.2g and a mean gestational age of 28.6 weeks. Of 300 GM assessments done, 157 were preterm assessments, 55 at term age and 88 at 12-14 weeks corrected age. At birth to 33 weeks PMA, 96% of GMs were abnormal and 4% normal. At 34-37 weeks PMA, 89%

of GMs were abnormal and 11% normal. All GMs were abnormal at term age. At 12-14 weeks corrected age, 7% of GMs were abnormal and 93% normal. On univariable analysis, lower birth weight (p=0.043), lower gestational age (p=0.017), intraventricular haemorrhage (IVH) grade IV (p<0.001) and time (PMA in weeks) (p<0.001) were associated with abnormal GMs. Birth weight (p=0.046) and time (PMA in weeks) (p<0.001) were the only variables inversely associated with abnormal GMs on multivariable analysis.

CONCLUSION

The results of this study indicated that GMs are predominantly abnormal prior to term age with a significant decrease in abnormality at 12-14 weeks corrected age. Assessment of preterm and term GM trajectories does not necessarily enable earlier identification of infants at risk for neurodevelopmental difficulties. It is thus not advised that resources be allocated to conduct preterm and term GM trajectories at TCH. Lower birth weight and lower PMA (time) were associated with increased odds for abnormal GMs. Infants with a lower birth weight should be targeted for more frequent follow up and neurological assessments as they remain the most at risk group for neurological deficits. Research on GM trajectories prior to term age and the association of risk factors with long term neurodevelopmental outcome is necessary for future comparison.

ABSTRAK

AGTERGROND

Premature baba's het 'n hoë risiko vir die ontwikkel van neurologiese afwykings, soos serebrale verlamming, en is afhanklik van vroeë identifisering en intervensie. Hulpbronne by Tygerberg Kinderhospitaal is beperk dus is klinici afhanklik van betroubare metodes van identifisering van hoë risiko baba's. Prof. Heinz Prechlt en sy medewerkers het 'n vinnige, bekostigbare en nie-indringende metode met goeie voorspellings vermoë ontwerp, om baba's met 'n risiko vir neurologiese aantastings, op 'n vroeë stadium te identifiseer. Hierdie metode is gebasseer of observasie van spontane bewegings en is ideaal vir gebruik in ontwikkelende lande waar hulpbronne skaars is. Daar is tans beperkte informasie beskikbaar oor die patroon van spontane bewegings voor volterm ouderdom asook die invloed van perinatale risikofaktore op hierdie bewegings.

DOEL

Om die koers van algemene bewegings vanaf geboorte tot 12-14 weke gekorrigeerde ouderdom, asook die effek van perinatale risikofaktore op die koers, te bepaal in baie lae geboortemassa en uiters lae geboortemassa premature baba's, opgeneem in die neonatale intensiewe eenheid van Tygerberg Kinderhospitaal, Kaapstad, Suid Afrika.

METODOLOGIE

'n Longitudinale, prospektiewe kohortstudie is uitgevoer deur Prechtl se metode van kwalitatiewe evaluaring van algemene bewegings tydens die volgende sleutel periodes toe te pas: geboorte tot 33 weke postmenstruele ouderdom, 34-37 weke postmenstruele ouderdom, volterm ouderdom asook 12-14 weke gekorrigeerde ouderdom. Gedetaileerde perinatale data is ingesamel. Resultate is deur middel van STATA weergawe 14 en IBM SPSS geanaliseer. 'n Logistieke regressie model is gebruik om die assosiasie tussen algemene bewegings uitkomste en perinatale risikofaktore te bepaal.

RESULTATE

Die studiegroep het bestaan uit 199 baba's met 'n gemiddelde geboortemassa van 1048.2g en gemiddelde gestasie ouderdom van 26.7 weke. Van die 300 algemene

bewegings assesserings is uitgevoer waarvan 157 preterm assesserings was, 55 tydens volterm en 88 tydens 12-14 weke gekorrigeerde ouderdom. Tydens geboorte tot 33 weke postmenstruele ouderdom, was 96% van die assesserings abnormaal en 4% normaal. Tydens 33-37 weke postmenstruele ouderdom was 89% van assesserings abnormal en 11% normaal. Alle assesserings was abnormaal tydens volterm assesserings. Tydens 12-14 weke gekorrigeerde ouderdom was 7% van assesseings abnormaal en 93% normaal. Met eenveranderlike anallise was laer geboortemassa (p=0.043), laer gestasie ouderdom (p=0.017), graad IV intraventrikulêre bloeding (p<0.000) asook tydsverloop (p<0.000) geassosieer met abnormale algemene bewegings. Tydens meerveranderlike analise was slegs geboortemassa (p=0.046) en tydsverloop (p,0.000) omgekeerd geassosieer met abnormale algemene bewegings.

GEVOLGTREKKING

Die resultate van die studie dui daarop dat algemene bewegings tydens die preterm tydperk hoofsaaklik abnormaal is, maar grootliks normaliseer teen 12-14 weke gekorrigeerde ouderdom. Dit is dus nie aanbevole dat hulpbronne op preterm beweging assesserings spandeer word nie. Lae geboortemassa en ‘n korter tydsverloop vanaf geboorte was geassosieer met ‘n grooter kans op abnormale algemene bewegings. Verdere navorsing in preterm algemene bewegings koerse en later ontwikkelingsuitkomsye is nodig vir toekomstige vergelykings.

ACKNOWLEDGEMENTS

The researcher would like to express her sincere appreciation and acknowledgement of the following people for their support and contribution throughout the course of the project and writing up of the thesis:

Ms. M Burger,
Supervisor, Physiotherapy Division, Stellenbosch University.
For continuous guidance, support and introducing me to general movement assessments. Your passion for this topic is inspirational. Thank you for your time and sacrifice!

Dr. JCF du Preez,
Co-supervisor, Neonatologist, Tygerberg Children's Hospital, Department of Paediatrics and Child Health, Stellenbosch University. For your advice and insight during the course of the study. Thank you for sharing your knowledge in the neonatal field with me.

Dr. JI van Zyl
Neurodevelopmentalist, Neonatal High Risk Clinic, Tygerberg Children's Hospital, Department of Paediatrics and Child Health.
Without your help with the assessments, follow-up appointments and logistical advice the study would not have been possible.

Ms. T Esterhuizen,
Statistician, Division of Epidemiology and Biostatistics, Stellenbosch University.
For analyzing the data and helping me understand the results.

Ms. J Couper,
Pediatric Occupational Therapist
Thank you for taking the time to edit my work

Colleagues at Marulize Swart Physiotherapy and all my friends
Thank you for your constant support and understanding.

My fiancé, Danie, and my parents
For your love and motivation

Most of all: the infants and their parents/guardians, to whom this study is dedicated

GLOSSARY

Definitions and Terminology

Corrected age

This is used when an infant is born before 37 weeks' gestation to correct the infants' age as if he/she was born at term age (Lindin, Paroli & Doron, 2013).

> For example: if an infant was born at 33 weeks' gestation and is now eight weeks old (chronological age), his/her PMA is 41 weeks and his/her corrected age is one week.

Extremely low birth weight (ELBW)

ELBW refers to an infant weighing 999g or less at birth (Hack, Wilson-Costello, Friedman, Taylor, Schluchter & Fanaroff, 2000).

Extremely preterm (EPT)

Infants born alive before 28 weeks' gestation (Pascal, Govaert, Oostra, Naulaers, Ortibus & Van den Broeck, 2018).

Gestational age

This is calculated from the first day of the last normal menstrual cycle period to the date of birth and is expressed in completed weeks (Engle, 2004).

Infant

An individual between one and 12 months of age (WHO, 2010).

Low birth weight (LBW)

LBW refers to an infant weighing 2499g or less at birth (Kramer, 1987).

Postmenstrual age (PMA)

This is calculated from the first day of the last menstruation before amenorrhea, and is counted in weeks (Engle, 2004).

Prematurity/preterm birth

This occurs if the infant is born alive before 37 weeks' gestation (259 days) (Goldenberg, Culhane, Iams & Romero, 2008).

Very low birth weight (VLBW)

VLBW refers to an infant weighing 1499g or less at birth (Pascal *et al.,* 2018).

Very preterm (VPT)

Infants born alive between 28 and 32 weeks' gestation (Pascal *et al.,* 2018).

Acronyms and abbreviations

APIB	Assessment of Preterm Infants' Behaviour
CDH	Congenital diaphragmatic hernia
CP	Cerebral Palsy
CT	Computed Tomography
ECMO	Extracorporeal membrane oxygenation
EEG	Electroencephalogram
ELBW	Extremely low birth weight
EPT	Extremely premature infants
FCR	Fetal circulatory redistribution
GMs	General movements
GMAs	General movement assessments
HINE	Hammersmith Infant Neurological Examination
IUGR	Intrauterine growth restriction
IVH	Intraventricular haemorrhage
MRI	Magnetic resonance imaging
NAPI	Neurobehavioural Assessment of the Preterm Infant
NBAS	Neonatal Behavioural Assessment Scale
NNNS	Neonatal Intensive Care Unit Network Neurobehavioural Scale
NPV	Negative predictive value
OA	Oesophageal atresia
PMA	Postmenstrual age
PPV	Positive predictive value
PROM	Premature rupture of membranes
PVL	Periventricular leukomalacia
SIP	Spontaneous intestinal perforation
SurgNEC	Surgical necrotizing enterocollitis
TCH	Tygerberg Children's Hospital
TIMP	Test of Infant Motor Performance
VEP	Visual Evoked Potentials
VLBW	Very low birth weight
VPT	Very Preterm Infants

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CHAPTER 1

INTRODUCTION

The incidence and the survival rate of premature births over the past decade have increased. This increase may be related to advances in both obstetric and neonatal care (Linsell, Malouf, Morris, Kurinczuk & Marlow, 2016). In a recent report by Pascal *et al.* (2018), it was estimated that globally, 11.1% of deliveries are premature births, which represents approximately 15 million infants born prematurely per annum. Unfortunately, the morbidity rate has increased due to neurodevelopmental delays, retinopathy of prematurity and chronic lung disease (Jarjour, 2015). Premature birth, which includes low birth weight infants, remains the leading cause for neurodevelopmental disability in early childhood, school age and in adulthood (Herskind, Greisen & Nielsen, 2015; Jarjour, 2015).

The incidence and severity of adverse outcomes in premature infants are related to birth weight, decreased gestational age and structural brain changes (Pascal *et al.,* 2018). In a recent systematic review by Pascal *et al.* (2018), it was estimated that 16.8% (95% CI 10.4-26.3) of very low birth weight (VLBW) infants developed some form of motor or cognitive delay by approximately two years of age. Furthermore, it was found that the prevalence of children with CP and those with motor and cognitive developmental delay were higher in extremely low birthweight (ELBW) infants compared to VLBW (Pascal *et al.,* 2018). Pascal *et al.* (2018), which reviewed research from 2006 until 2016, found that the prevalence of children with CP had decreased in extremely preterm infants (EPT). As a result of improved neonatal care in recent years, the overall prevalence rate of CP in EPT was 10.0% (Pascal *et al.,* 2018). Jarjour (2015) investigated the outcome of EPT infants and found that the rates of survival without an impairment or minimally impaired, range from 6% to 20% for infants born at ≤25 weeks' gestation and <5% for infants born at 22 and 23 weeks' gestation.

Amongst the motor impairments reported in preterm infants, CP remains the most common (Spittle & Orton, 2014). The definition of CP refers to "a group of permanent developmental and movement disorders leading to activity limitations, as well as a variety of secondary complications such as sensory disorders, epilepsy and intellectual disability"

(Rosenbaum, Paneth, Leviton, Goldstein, Bax, Damiano, Dan & Jacobsson, 2007). The presentation of CP in preterm infants differs from those born at term age and diagnosed with CP. This difference relates to topography (hemiplegia, diplegia and quadriplegia) and motor type (hypotonia, ataxia, dyskinesia and spastic) (Spittle & Orton, 2014). A meta-analysis by Himpens *et al.* (2008), reported spastic CP as the predominant motor type in both preterm (96%) and term (82%) children. Spastic diplegia was the most prevalent subtype (60%) of CP reported in preterm children (Himpens, Van den Broeck, Oostra, Calders & Vanhaesebrouck, 2008).

Historically CP was diagnosed between the ages of 12 and 24 months, but experts have proposed that CP can be accurately diagnosed before six months corrected age (Novak, Morgan, Adde, Blackman, Boyd, Brunstrom-Hernandez, Cioni, Damiano, Darrah, Eliasson & de Vries, 2017). The first 24 months in a child's life are regarded as a critical period for the development of the corticospinal tract (Morgan, Darrah, Gordon, Harbourne, Spittle, Johnson & Fetters, 2016), therefore, early activity-based interventions are imperative for optimizing motor outcomes (Friel, Chakrabarty, Kuo & Martin, 2012). Early identification and intervention in infants at risk for or diagnosed with CP within the first year post birth is associated not only with improved motor developmental outcomes, but also with enhanced cognitive function (Spittle, Thompson, Brown, Treyvaud, Cheong, Lee, Pace, Olsen, Allinson, Morgan & Seal, 2014; Hadders-Algra, Boxum, Hielkema, & Harmer, 2017).

In Africa, the prevalence of children with CP is higher than the estimated 2-2.5 cases per 1000 live births reported in European and American studies (Gottlieb, Maenner, Cappa & Durken, 2009; Donald, Samia, Kakooza-Mwesige & Bearden, 2014). The screening and identification of developmental disabilities in high risk infants in Africa has been inadequate (Donald *et al*., 2014). Limited resources at TCH have minimized access to expensive technical evaluation procedures and comprehensive, time-consuming neurological examinations in order to detect brain dysfunction in high-risk premature infants (Pieper, Smith, Maree & Pohl, 2003). As a result of limited available beds and staff as well as the high demand, high-risk premature infants are discharged when there is adequate weight gain and are medically stable, most often at 34-36 weeks PMA. Mothers residing in poor rural areas have inadequate access to follow-up medical care after discharge. Therefore, premature infants who are at risk for neurodevelopmental difficulties are often lost to follow-up and effective interventions. As a result, these infants

may develop secondary complications such as muscle/tendon contractures, bony torsion, hip displacement and spinal deformities (Burger, Frieg & Louw, 2011). Thus, an inexpensive, reliable and non – invasive method for early identification of CP or other neurological disorders is warranted.

Professor Heinz Precthl and his co-workers developed such a method in the early 1990s. This method is based on the observation and assessment of spontaneous movement patterns in young infants (Burger *et al.,* 2011). They concluded that the quality of spontaneous movement patterns in infants, referred to as GMs, reflects the integrity of the young nervous system (Einspieler & Prechtl, 2005). GMs are age specific and can be observed from as young as nine weeks PMA until 20 weeks post-term age. Various systematic reviews have validated the qualitative assessment of GMs as a reliable predictor of CP (Burger & Louw, 2009; Darsaklis, Snider, Majnemer & Mazer, 2011; Novak *et al.,* 2017). Specific movements are characterised as high risk for CP during 12-15 weeks post-term age or known as the fidgety period (Einspieler, Precthl, Bos, Ferrari & Cioni, 2004).

To date, only one study on the predictive validity of GMs has been conducted in a South African setting. Burger *et al.* (2011) conducted a study at TCH in Cape Town to assess the predictive validity of the qualitative assessment of fidgety movements at 12 weeks corrected age on neurological outcome of VLBW and ELBW preterm infants. The findings demonstrated that the absence of fidgety movements predicted the development of CP with a sensitivity of ≥71% in VLBW and ELBW infants. Furthermore, normal fidgety movements were reported as a predictor of further normal neurological development with a ≥89% specificity (Burger *et al*., 2011).

Although the qualitative assessment of GMs have been widely reported and the predictive value well described, most studies examined GMs at term age as well as at 12-15 weeks post-term age (Spittle, Brown, Doyle, Boyd, Hunt, Bear & Inder, 2008; Spittle, Spencer-Smith, Cheong, Eeles, Lee, Anderson & Doyle, 2013; Dostanic, Sustersic & Paro-Panjan, 2018). There have been only four studies that reported on GM trajectories (multiple or serial assessments of GMs) during preterm age (Bos, van Loon, Hadders-Algra, Martijn, Okken & Precthl, 1997c; De Vries, Erwich & Bos, 2008; De Vries & Bos, 2010; Olsen, Brown, Eeles, Lee, Anderson, Cheong, Doyle & Spittle, 2015). There is a limited understanding of preterm GM trajectories seen in this high-risk preterm population (Olsen

et al., 2015). Perinatal factors, such as IVH, necrotizing enterocolitis, bronchopulmonary dysplasia and postnatal corticosteroids may have an influence on the early neurodevelopment of the preterm infant. A trajectory of GMAs is more accurate to predict an infant's neurodevelopmental outcome compared to single assessments (Einspieler & Prechtl, 2005). The quality of GMs during preterm age, assessed as a single assessment, is fairly to moderately associated with later functional motor outcomes (Manacero, Marschik, Nunes & Einspieler, 2012).

The high predictive validity of GMs rely on developmental trajectories. A once off assessment is not reliable as abnormal GMs can be transient and/or present for several weeks during the preterm and post-term age (Manacero *et al*., 2012). A knowledge and understanding of GM trajectories and the influence of adverse perinatal factors is important to compare and analyse in future studies. More importantly, the purpose of this study is to determine if the assessment of GM trajectories will enable earlier prediction and identification of high-risk infants at risk for neurodevelopmental difficulties. The intention of this study, which is perhaps a first in South Africa, will be to inform early assessment practices of high-risk premature infants at TCH.

CHAPTER 2

LITERATURE REVIEW

2.1 Introduction

In this chapter, Prechtl's method of the qualitative assessment of GMs in preterm, term and young infants will be discussed, including: historical development of the assessment of the young nervous system, characteristics of normal and abnormal GMs and the psychometric properties of GMAs. The influence and association between perinatal factors, GMs and neurodevelopment of the preterm infant will be described.

A systematic search of the following databases was done via the Stellenbosch University Library services: Pubmed; ProQuest; Science Direct; Scopus; Cochrane and Cinahl. The list of references on the General Movement Trust website (http://general-movements-trust.info) were also reviewed. All relevant articles were sourced, and an overview of available literature was undertaken.

2.2 Prechtl's Method on the Qualitative Assessment of General Movements (GMs) in Preterm, Term and Young Infants

2.2.1 Historical development of the assessment of the young nervous system

Neurological testing in young high-risk infants were first developed in the middle of the twentieth century and mainly consists of postural reflex testing and the assessment of muscle tone (Hadders-Algra, 2001). In the early 1970's, after having worked in the field of infant neurology for 25 years, Heinz Prechtl became curious about the development of spontaneous movement patterns in preterm and full-term infants. He believed that birth could not be the starting point and that spontaneous movement patterns had a prenatal history (Precthl & Hopkins, 1986). At the time, ultrasound technology was not advanced enough to allow the observation of fetal movements. Prechtl decided to follow an unusual approach by observing, with the unaided eye, a group of low risk preterm infants. He documented the endogenous movement patterns displayed in unstimulated preterm infants which was the start of documenting the GMAs (Prechtl, Fargel, Weinmann & Bakker, 1979). The advancement of ultrasound technology in the 1980's allowed for

prolonged and repeated observations of fetal spontaneous movement patterns. This confirmed that postnatal spontaneous movement patterns have indeed a long prenatal history (de Vries, Visser & Prechtl, 1982; de Vries, Visser & Prechtl, 1985; de Vries, Visser & Prechtl, 1988). Heinz Prechtl and his co-workers (Christa Einspieler, Arend Bos, Fabrizio Ferrari and Giovani Cioni) named these spontaneous prenatal and postnatal movement patterns GMs (Precthl *et al.,* 1979; Prechtl, 1990).

2.2.2 The developing nervous system and general movements (GMs)

Human brain development is a continuous and complex process that involves a constant interaction between genes and environment. The highest rate of neurogenetic events take place during the fetal period and the first two postnatal years (Hadders-Algra *et al.,* 2017). Brain plasticity, especially before term age, enables various age related neurobiological modifications. These neurobiological changes have important implications for the prediction of normal development or developmental disorders at an early age (Zuk, 2011).

At seven weeks PMA the first fetal movement, namely side flexion of the neck emerges. Complex and variable GMs involving the whole body can be observed from nine to ten weeks PMA (Hadders-Algra *et al.,* 2017). GMs are the most frequently occurring and most complex of all motor patterns (Prechtl, 1990). These GMs are not triggered by sensory input (Einspieler, Bos, Libertus & Marschik, 2016). GMs are a major expression of the developing brain and they form the cornerstone of early development (Hadders-Algra *et al.,* 2017).

Remarkably, there are hardly any changes in the form and pattern of spontaneous GM patterns in the first weeks after birth, despite a fourfold increase in gravity and profound changes in the environmental circumstances (Einspieler & Prechtl, 2005). In the healthy preterm infant, the continuation of spontaneous GM patterns remain similar to an infant born at term age, when using the corrected age of the preterm infant (Cioni & Prechtl, 1990). After birth, GMs can be observed until three to four months post-term, and thereafter gradually replaced by voluntary, goal-directed and anti-gravity movements (Hadders-Algra, 2001).

2.2.3 Characteristics of normal general movements (GMs)

Heinz Prechtl and his co-workers defined GMs as “movement patterns that involves the entire body and presents in variable sequences of arm, leg and trunk movements” (Prechtl, 1990, p.152). GMs have a gradual onset and end, wax and wane in force, intensity and speed. Rotations along the axis of the limbs and slight changes in direction of movements make them fluent and elegant. This creates the impression of complexity and variability. GM patterns can vary from a few seconds to a couple of minutes (Prechtl, 1990).

Normal GMs can be observed during three defining age periods. Before term age, they are referred to as preterm or ‘fetal GMs’. From term age until four weeks post-term age they are called ‘writhing movements’. From six to nine weeks post-term age, these writhing movements gradually fade and are replaced by fidgety movements. Fidgety movements are a continuum of small amplitude movements. They can be observed up to 20 weeks post-term age and are followed by intentional and antigravity movements (Einspieler & Prechtl, 2005). Figure 2.1 describes the development of GMs in the infant.

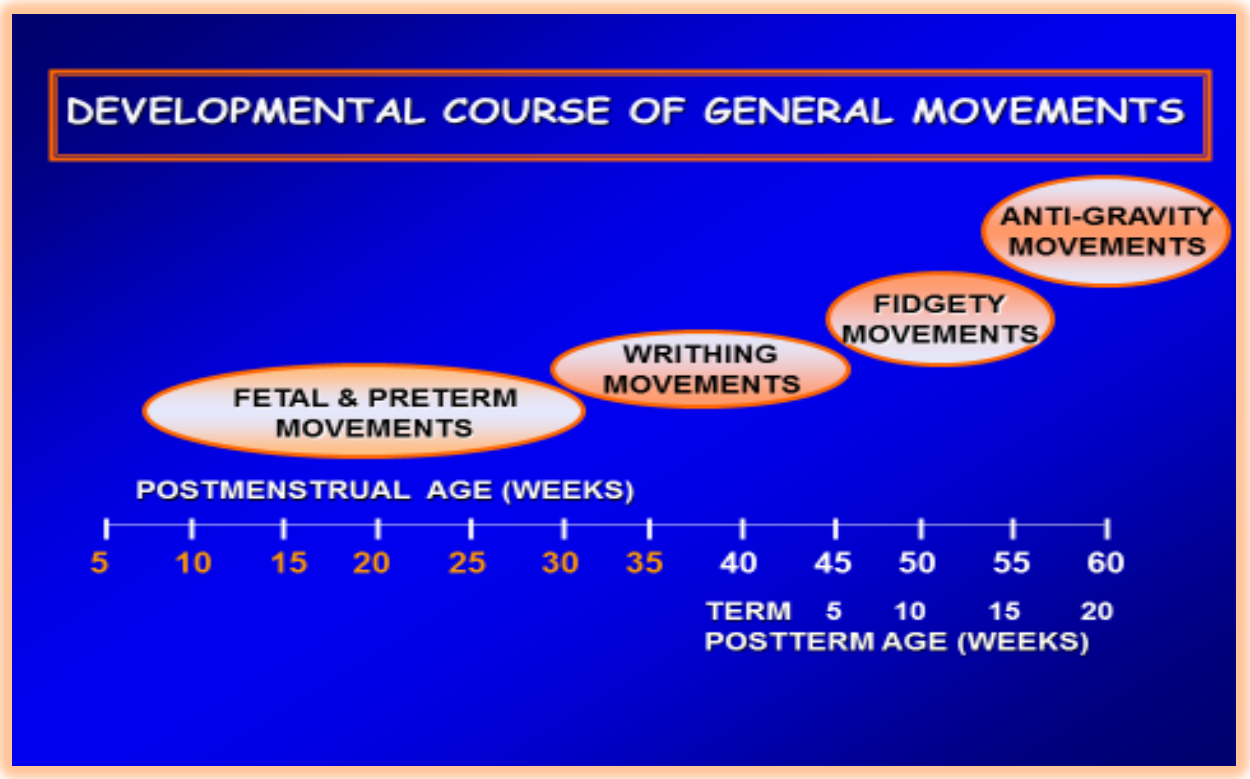

Figure 2.1 Developmental course of general movements (GMs)

- Preterm GMs:

In preterm infants, GMs may be of large amplitude and of fast speed (Cioni & Prechtl, 1990). No difference has been noted between fetal and preterm GMs. This suggests that neither gravity postnatally nor maturation has an effect on GMs.

- Writhing GMs:

From term age and until four weeks post-term, GMs are referred to as writhing movements. These movements are characterized by small to moderate amplitude and slow to moderate speed. Their elliptical presentation creates the impression of a writhing quality (Prechtl & Hopkins, 1986; Prechtl, Einspieler, Cioni, Bos, Ferrari & Sontheimer, 1997; Einspieler & Prechtl, 2005).

- Fidgety GMs:

There is major neural transformation from six to nine weeks post-term. Fidgety movements start to emerge as writhing movements gradually disappear. Fidgety movements are small motions of moderate speed and variable acceleration in all directions of the neck, trunk and limbs. These movements are present and continual in the awake infant and absent during fussing or crying (Precthl *et al.,* 1997). Fidgety movements can be observed until 20 weeks post-term when intentional and antigravity movements begin to dominate (Prechtl *et al.,* 1997). Initially, between six to eight weeks, fidgety movements are isolated. From 12 to 15 weeks the frequency of fidgety movements increases, thus the optimum time for observation and assessment (Einspieler *et al.,* 2004; Prechtl, 1997).

2.2.4 Characteristics of abnormal general movements (GMs)

Normal GMs are characterized by complexity, variation and fluency. Fluency refers to coordinated muscle patterns. Variations in active muscles as well as the timing and quantity of muscle activation represent movement patterns consisting of fluency and quality (Prechtl, 1990).

Impairments or disruptions in the young nervous system results in GMs losing their complexity, variation and fluency. This is reflected in an absence or decrease of variation in muscle coordination. Abnormal movement patterns consist of either a stereotyped

synchronous activation of participating muscles or a stereotyped pattern of reciprocal activity (Hadders-Algra, van Nieuwendijk, Maitijn & van Eykern, 1997).

Prechtl describes abnormal GMs during the preterm and the writhing period (term to four weeks post-term age) as poor-repertoire, cramped-synchronized or chaotic. This describes abnormal GMs for the preterm, term and post-term age (four weeks post-term). Fidgety movements (from six to nine weeks until 20 weeks post-term age) are classified as either abnormal fidgety or absent fidgety movements (Prechtl, 1997; Prechtl *et al.,* 1997; Einspieler & Prechtl, 2005).

- Poor-repertoire GMs:

This form of abnormal GMs can be observed during preterm, term and early post-term age. GMs that are described as poor-repertoire are repetitive, and the movements in the different body parts do not occur in a complex manner as seen in normal GMs (Ferrari, Cioni & Prechtl, 1990; Einspieler, Prechtl, Ferrari, Cioni & Bos, 1997; Einspieler & Prechtl, 2005). Poor-repertoire GMs is frequently observed in preterm infants and in infants with ultrasound brain abnormalities. Poor-repertoire GMs can develop later into normal, abnormal or absent fidgety movements. Thus, the predictive value of poor-repertoire GMs is low (Precthl, 1997; Einspieler *et al.,* 2004; Einspieler & Prechtl, 2005).

- Cramped-synchronized GMs:

Cramped-synchronized GMs are abnormal movement patterns and can be observed from 34 weeks PMA. Movements appear rigid and lack the normal smooth and fluent character, all limb and trunk muscles contract and relax simultaneously (Ferrari *et al.,* 1990; Prechtl, 1997). If this movement pattern is observed consistently over a number of weeks, it has a high predictive value for the development of severe spastic CP (Ferrari *et al.,* 1990; Precthl, 1997; Einspieler, Cioni, Paolicelli, Bos, Dressler, Ferrari, Roversi & Prechtl, 2002).

- Chaotic GMs:

This movement pattern is rare but can be observed during preterm, term and post-term age. Movements of all the limbs are continuously jerky and of large amplitude. The movement patterns occur in a chaotic order and lack smoothness and fluency. Infants that display chaotic GMs during the preterm or term age often develop cramped-synchronized movements resulting in spastic CP (Bos, van Asperen, de Leeuw & Prechtl,

1997a; Bos *et al.,* 1997a; Ferrari, Prechtl, Cioni, Roversi, Einspieler, Gallo, Paolicelli & Cavazzuti, 1997).

- Abnormal fidgety movements:

These movements resemble normal fidgety movements, but their amplitude, speed and jerkiness are greatly exaggerated. Abnormal fidgety movements are rarely observed and have very low predictive value (Prechtl, 1997; Prechtl *et al.,* 1997; Einspieler *et al.,* 2002; Einspieler & Prechtl, 2005).

- Absent fidgety movements:

If fidgety movements are not observed from nine to 20 weeks post-term age, it is referred to as the "absence of fidgety movements". The absence of fidgety movements is of high predictive value for later neurological impairments, such as CP. Cramped-synchronized movements start to develop at 34 weeks PMA. If cramped-synchronized movements are present at three to four months post-term age, fidgety movements will be absent (Prechtl, 1997; Prechtl *et al.,*1997; Einspieler *et al.,* 2002).

2.2.5 Psychometric properties of general movement assessments (GMAs)

In the neonatal setting, specialists are faced with the challenge of early identification of infants who are most at risk for the development of neurological disorders such as CP. Assessment tools for neonatal neurodevelopment need to be valid and reliable. They must also be applicable from the prenatal until early postnatal period (Noble & Boyd, 2012). To ensure that all infants are assessed under similar conditions, assessment tools must have a consistent, documented set of procedures for administering, criterion testing and scoring (Noble & Boyd, 2012). Longitudinal infant neuromotor assessments are more predictive and useful than single assessments, as they describe information on maturation, recovery from injury and reorganization. Longitudinal assessments assess an infant's developmental trajectory over time (Brazelton & Nugent, 1995; Barbosa, Campbell, Sheftel, Singh & Beligere, 2003; Dubowitz, Ricciw & Mercuri, 2005).

Noble & Boyd (2012) conducted a systematic review analyzing the validity of assessment tools used in preterm infants until four months corrected age. They found that GMAs have the best sensitivity and specificity for predicting outcome at 12 months when compared to the following assessment tools: Assessment of Preterm Infants' Behaviour (APIB), Neonatal Intensive Care Unit Network Neurobehavioural Scale (NNNS), Test of Infant

Motor Performance (TIMP), Neurobehavioural Assessment of the Preterm Infant (NAPI), Dubowitz Neurological Assessment of the Preterm and Full-term Infant (Dubowitz), Neuromotor Behavioural Assessment (NMBA), and the Brazelton Neonatal Behavioural Assessment Scale (NBAS).

A recent systematic review by Craciunoiu & Holsti (2017) reported specifically on the predictive validity of standardized assessments completed during the preterm and very preterm developmental period. Four studies using GMAs were included in the review and showed a consistent trend of high negative predictive values (NPV) of 90-94% and lower positive predictive values (PPV) of 21-36% across a range of gestational ages. The methodological quality of the four studies ranged from poor (Nakajima, Einspieler, Marschik, Bos & Prechtl, 2006) to good (Garcia, Gherpelli & Leone, 2004; de Vries & Bos, 2010; Manacero *et al.,* 2012). One study reported 100% sensitivity in the preterm, 78% in term and 75% in post-term period, and 44% specificity in the preterm, 50% in term and 67% in post-term period (Garcia *et al.,* 2004).

A systematic review conducted by Burger & Louw (2009) reported on the predictive validity of GMs for the four key age periods. The sensitivity in the preterm age ranged from 50 to 75% and the specificity from 45 to 84% (Cioni, Prechtl, Ferrari, Paolicelli, Einspieler & Roversi, 1997a; Ferrari *et al*., 2002; Constantinou, Adamson-Macedo, Mirmiran, Ariagno & Fleisher, 2007). At term age, five studies reported a sensitivity ranging between 68 to 92% and the specificity was reported as 58.8 to 92% (Cioni, Ferrari, Einspieler, Paolicelli, Barbani & Prechtl, 1997b; Cioni *et al*., 1997a; Ferrari *et al*., 2002; Paro-Panjan, Sustersic & Neubauer, 2005; Stahlman, Härtel, Knopp, Gehring, Kiecksee & Thyen, 2007). During the fidgety period (12-15 weeks post-term age), seven studies reported on the sensitivity, ranging between 88.9 and 100% while the specificity ranged from 43 to 87% (Cioni *et al*., 1997a; Cioni *et al*., 1997b; Ferrari *et al*., 2002; Seme-Ciglenečki, 2003; Paro-Panjan *et al*., 2005; Stahlman *et al*., 2007; Romeo, Guzzetta, Scoto, Cioni, Patusi, Mazzone & Romeo, 2008).

Forty international experts conducted a recent systematic review and developed an international clinical practice guideline, which suggests that CP can be accurately predicted before the corrected age of six months (Novak *et al.,* 2017). The tools with the best predictive validity for detecting CP before five months corrected age were Prechtl's qualitative assessment of GMs (98% sensitivity), the Hammersmith Infant Neurological

Examination (HINE) (90% sensitivity) and neonatal magnetic resonance imaging (MRI) (86%-89% sensitivity). They strongly recommend that the most accurate method for early detection of CP in high risk infants younger than five months corrected age, is GMs combined with neuroimaging (MRI). GM assessment is recommended as a tool for neuro-assessment in settings where MRI is not available nor affordable, for example in low and middle-income countries (Novak *et al.,* 2017). For the assessment of GM trajectories, three to four key age periods are generally used namely, before term age, at term equivalent age, from term age to four weeks post-term age and during the fidgety movements period (8-20 weeks post-term age) (Burger & Louw, 2009).

The quality of GMs is assessed by means of video recordings and based on visual Gestalt perception of the observer (Bernhardt, Marbacher, Hilfiker & Radlinger, 2011). Gestalt perception can be understood as "able to take into account a greater number of individual details and more relationships between these than in any rational calculation" (Lorenz, 1971). Visual Gestalt perception is used whenever static or dynamic images are globally assessed and pattern recognition is utilized during this procedure (Einspieler *et al.,* 2004).

There is substantial evidence that GMA has very good inter- and intra-observer agreement (kappa values > 0.8) (Bos, Martijn, van Asperen, Hadders-Algra, Okken & Prechtl,1998; Cioni, Bos, Einspieler, Ferrari, Martijn, Paolicelli, Rapisardi, Roversi & Prechtl, 2000; Fjørtoft, Einspieler, Adde & Strand, 2009). These studies have been conducted by senior and highly skilled GMA licensed tutors (http://general-movements-trust.info/48/licenced-tutors) and members of the GM Trust. Studies not conducted by members of the GM trust reported very good inter- and intra-observer agreements (van Kranen-Mastenbroek, van Oostenbrugge, Palmans, Stevens, Kingma, Blanco, Hasaart & Vles, 1992; Brown, Griesen, Haughsted & Jonsbo, 2016). A fair to almost perfect inter-observer agreement was found (kappa values 0.36-0.84) by van Kranen-Mastenbroek *et al.* (1992), while Brown *et al.* (2016) confirmed substantial to almost perfect agreement (kappa values 0.71-0.85).

In order to improve reliability within the clinical setting, Bernhardt *et al.* (2011) advises that video assessments are conducted by at least two trained GM observers and the results openly discussed to reach an agreement. The assessors are advised to use the technique on a regular basis (Brown *et al.,* 2016). Furthermore, factors that affect the observer's Gestalt perception should be avoided (Einspieler *et al.,* 2004). These include

audio during the assessment, interferences by caregivers and siblings, toys or a colourful blanket. Observer fatigue also interferes with visual Gestalt perception and it is advised that an observer should not assess for longer than 45 minutes at a time (Einspieler *et al.,* 2004).

Crowle *et al.* (2017) investigated the inter-observer agreement of GMA in preterm infants following surgery. This study criticized the use of Cohen's kappa statistic to report inter-observer reliability in GMA, due to the high proportion of normal GMs occurring in the fidgety period (12-15 weeks post term age). Although the agreement of 86% between observer one and two in the fidgety period was very high, the kappa was calculated to be 0.32. This was due to the high number of infants (88%) rated as 'normal' (Crowle *et al.* 2017). This unexpected result is known as the 'paradox of kappa'; if the prevalence of normal GMs is high, the correction process will convert a high percentage agreement into a low kappa (Gwet, 2008). Crowle *et al.,* (2017) opted to use Gwet's AC1 statistic to interpret inter-observer agreement coefficients, as an alternative to the kappa. The Gwet's AC1 statistic adjusts for chance agreement more appropriately than kappa (Nishiura, 2010) and gives a less deviating perspective of interrater agreement (Mulligan, McGuffie, Coyner & Khazzam, 2015). Crowle *et al.* (2017) found moderate to substantial agreement between assessors during the writhing period (term age to 4 weeks post-term). The median AC1 statistics were 0.60 (range 0.58 to 0.74) and 0.59 (range 0.50 to 0.63) respectively. A near perfect agreement was found between observers during the fidgety period (Crowle, Walker, Galea, Novak & Badawi, 2017).

2.3 The influence of perinatal factors in the neurodevelopment of the preterm infant

Preterm infants are at high risk for the development of CP, which may include motor, cognitive, visual and auditory impairments, as well as behavioural problems (Xiong, Gonzalez & Mu, 2012; Linsell *et al.,* 2016). The costs of neonatal intensive care are high and preterm infants are more likely to require additional health care services post discharge (Linsell *et al.,* 2016). Identification of all factors that might influence long-term outcomes in preterm infants is important to guide health care practitioners about treatment and intervention (Xiong *et al.,* 2012; Linsell *et al.,* 2016).

Intra and extra-uterine factors can influence the neurodevelopment outcomes of young infants. The maternal factors include maternal obesity (Stothard, Tennant, Bell & Rankin,

2009; Torloni, Beltran, Daher, Widmer, Dolan, Menon, Bergel, Allen & Merialdi, 2009; Cnattingius, Villamor, Johansson, Bonamy, Persson, Wikström & Granath, 2013), tobacco and cocaine use during pregnancy (Shah & Bracken, 2000; Frank, Augustyn, Knight, Pell & Zuckerman, 2001), maternal depression (Grote, Bridge, Gavin, Mellville, Iyengar & Katon, 2010), young or advanced maternal age (Huang, Sauve, Birkett, Fergusson & van Walraven, 2008; Blencowe, Cousens, Oestergaard, Chou, Moller, Narwal, Adler, Garcia, Rohde, Say & Lawn, 2012), maternal periodontal disease (Ide & Papapanou, 2013) and pre-existing maternal diabetes (Flenady, Koopmans, Middleton, Frøen, Smith, Gibbons, Coory, Gordon, Ellwood, McIntyre & Fretts, 2011).

Various intra-uterine factors affect the outcome of the infant and include intrauterine growth restriction (Levine, Grunau, McAuliffe, Pinnamaneni, Foran & Alderdice, 2014; Murray, Fernandes, Fazel, Kennedy, Villar & Stein, 2015), preeclampsia (Backes, Markham, Moorehead, Cordero, Nankervis & Giannone, 2011), birth asphyxia, (van Handel, Swaab, de Vries & Jongmans, 2007), fetal inflammatory response syndrome (Romero, Gotsch, Pineles & Kusanovic, 2007) infections such as chorioamnionitis (Shi, Ma, Luo, Bajaj, Chawla, Natarajan, Hagberg & Tan, 2017) and microbial invasion of the amniotic cavity (Romero *et al.,* 2007).

There are also multiple extra-uterine factors that play a significant role in infant outcomes. These include sepsis (Mwaniki, Atieno, Lawn & Newton, 2012), IVH (Obladen, Metze, Henrich, Atkas, Czernik & Schulz-Baldes, 2008; Klebermass-Schrehof, Czaba, Olischar, Fuiko, Waldhoer, Rona, Pollak & Weninger, 2012), periventricular leukomalacia (PVL) (Woodward, Anderson, Austin, Howard & Inder, 2006; Bass, 2011), necrotizing enterocolitis (Xiong *et al.,* 2012), spontaneous intestinal perforation surgery and other surgeries (Rees, Pierro & Eaton, 2007), bronchopulmonary dysplasia (Gough, Spence, Linden, Halliday & McGarvey, 2012), retinopathy of prematurity, mechanical ventilation (Allen, 2008), jaundice (Shapiro, 2003) and the use of opioids (Davidson & Flick, 2013).

In a recent systematic review by Linsell *et al.* (2016), perinatal factors related to the development of CP, impaired fine or gross motor skills and neurological dysfunction were investigated. There was a strong association for the development of CP post brain injury during the neonatal period. IVH and/or PVL had the strongest causal factor to CP. Postnatal steroids administered during the neonatal period was also associated with a CP diagnosis. There was some evidence for a correlation between male infants and

motor impairment. There was some evidence, although conflicting, in the relationship between male infants and CP. Lower gestational age was not found to be predictive of CP. Impaired fine or gross motor skills was found to be affected by the use of postnatal steroids (Linsell *et al.,* 2016). Anesthesia and surgery during the neonatal period were found to have an effect on neurodevelopment (Taddio, Katz, Ilersich & Koren, 1997; Sun, 2010; Sanders, Hassel, Davidson, Robertson & Ma, 2013).

A review conducted by Xiong *et al.* (2012) reported that infants with necrotizing enterocolitis requiring surgery was associated with significant growth delay and adverse neurodevelopmental impairments at the corrected age of 18 to 22 months. Xiong *et al.* (2011) agreed with the findings by Linsell *et al.* (2016), which listed PVL, IVH, male infants and the administration of postnatal steroids as predictors for some form of developmental delay in preterm infants.

A systematic search was conducted for relevant articles relating to the influence of perinatal factors in the short and long-term neurodevelopment of the preterm infant. The search was conducted during January 2018 and the following six computerised bibliographic databases were accessed through the Stellenbosch University Library services: Pubmed; ProQuest; Science Direct; Scopus; Cochrane and Cinahl. A search strategy was compiled for each database depending on the function. No date limit was applied to the databases.

The following main key search terms were used and combined as search strings: “periventricular leukomalacia”, “intraventricular haemorrhage”, “surgical necrotizing enterocolitis”, “intrauterine growth restriction”, “neonatal surgery”, anaesthesia, gender, steroids, development, neurodevelopment, “general movements”, “general movement assessments” and “premature infant”.

The most common perinatal factors in the short and long-term neurodevelopment of the preterm infant will be discussed below.

2.3.1 Intraventricular haemorrhage (IVH) and periventricular leukomalacia (PVL)

Various types of brain injury can occur as a result of hemodynamic changes in premature infants, with the most common being IVH and PVL (Barkovich, 2005). Infants with both IVH and PVL have a much worse cognitive and motor outcome than those with mild or

no IVH (Chuang, Hsu, Liu & Wang, 2004). A systematic review by Linsell *et al.* (2016) reported that IVH gr III and IV with and without PVL, was highly predictive of CP.

2.3.1.1 Intraventricular haemorrhage (IVH)

The incidence of IVH in preterm infants has decreased over the past decades and ranges between 15% and 45%. ELBW infants have a significantly higher incidence than VLBW infants (Chuang *et al.,* 2004; Patra, Wilson-Costello, Taylor, Mercuri-Minich & Hack, 2006; Obladen *et al.,* 2008; Klebermass-Schrehof *et al.,* 2012). The incidence of a severe disability in ELBW infants after IVH is significantly higher (Catto-Smith, Yu, Bajuk, Orgill & Astbury, 1985; Chuang *et al.,* 2004). Developmental impairment increases significantly with increasing grades of IVH (Whitelaw, 2011; Klebermass-Schrehof *et al.,* 2012). Diagnosis of IVH is primarily done via brain imaging studies, such as cranial ultrasonography (Annibale & Hill, 2006). The classification of IVH from grade I to IV was first recorded by Papile *et al.* (1978) utilizing computed tomography (CT) scans. Grade I IVH is confined to the subependymal germinal matrix. Grade II, IVH involves the lateral ventricles without ventricle dilatation. Grade III, IVH presents with ventricle dilatation and grade IV IVH has parenchymal involvement caused by venous infarction (Papile, Burstein, Burstein & Koffler, 1978). Kobayashi *et al.* (2015) retrospectively reviewed the MRI studies of 381 patients with CP who were born preterm. They concluded that cerebellar injury alone might not predict a patient's motor development but also supratentorial lesions, such as white matter and basal ganglia lesions. Furthermore, all patients with cerebellar injury had speech impairments (Kobayashi, Wakusawa, Inui, Tanaka, Kobayashi, Onuma & Haginoya, 2015).

No association has been found between cerebellar volume and motor neurological signs. However, significant associations were found between cerebellar volume and cognitive function in adolescents born very preterm (Allin, Matsumoto, Santhouse, Nosarti, AlAsady, Stewart, Rifkin & Murray, 2001; Kobayashi *et al.,* 2015). No difference in neurodevelopmental outcome was found between very preterm infants with grade I and II germinal matrix-intraventricular hemorrhage (GMH-IVH) on cranial ultrasound compared to controls without GMH-IVH (Reubsaet, Brouwer, van Haastert, Brouwer, Koopman, Groenendaal & de Vries, 2017).

In a survey study by Volpe (2009) it was estimated that 50% of grade III IVH survivors had a neurological deficit (Volpe, 2009). Futagi *et al.* (2006) reported that 23% of survivors

with grade III IVH developed CP compared to 17% of those with grade II IVH and 7% of those who had grade I IVH (Futagi, Toribe, Ogawa & Suzuki, 2006). In infants presenting with grade IV IVH the risk for future disability is related to the size and location of the parenchymal injury (Whitelaw, 2011). Extensive unilateral infarction involving the frontal, parietal and occipital areas is associated with severe motor deficits (spastic hemiplegia & asymmetric quadriplegia) in more than 80% of cases (Whitelaw, 2011).

2.3.1.2 Periventricular leukomalacia (PVL)

Focal necrosis and gliosis of the periventricular white matter, commonly referred to as PVL is the most common form of brain injury in preterm infants (Bass, 2011). Neuroimaging and neuropathological studies defined two forms of PVL; cystic and diffuse. Cystic PVL is marked by focal cystic necrotic lesions deep within the periventricular white matter, involving all cellular elements. The cysts can be a few millimeters in size and evolve over time (Volpe, 2009). Cystic PVL may be visible in the first week postnatally, although cysts generally appear two to four weeks thereafter (De Vries, van Haastert, Rademaker, Koopman & Groenendaal, 2004). Diffuse PVL is the most common form of brain injury and a major cause of severe neurodevelopmental impairment and cognitive deficits in the preterm population (Back, Luo, Borenstein, Levine, Volpe & Kinney, 2001; Maalouf, Duggan, Counsell, Rutherford, Cowan, Azzopardi & Edwards, 2001; Counsell, Allsop, Harrison, Larkman, Kennea, Kapellou, Cowan, Hajnal, Edwards & Rutherford, 2003). Various studies using MRI have shown a high incidence of diffuse PVL in preterm infants at term age, with reported rates as high as 70% (Maalouf *et al.,* 2001; Inder, Anderson, Spencer, Wells & Volpe, 2003; Woodward *et al.*, 2006).

2.3.2 Anesthesia and neonatal surgery

A systematic review by Sanders *et al.* (2013) on the effects of anesthesia and surgery during the neonatal period on neurodevelopment, concluded that the evidence was weak due to too few human studies on this topic. Another review confirmed that the clinical evidence on the relationship between anesthesia and the developing brain is scarce and further studies are needed (Istaphanous & Loepke, 2009). Neonatal pain, induced by surgery, is known to contribute to long-term consequences in behavioural difficulties (Taddio *et al.,* 1997; Sun, 2010). Suppression of synaptic activity during anesthetic injury can result in a redundant neuron and lead to apoptosis or cell death. This is consistent with the known effects of synaptic signaling in neurodevelopment (Olney, Young,

Wozniak, Ikonomidou & Jevtovic-Todorovic, 2004). A meta- analysis by DiMaggio *et al.* (2012), found evidence from epidemiologic studies that exposure to anesthesia and surgery during early childhood led to an elevated risk of adverse behavioural or developmental outcomes (Dimaggio, Sun, Ing & Li, 2012).

Perioperative neurologic complications following neonatal cardiac surgery is low (1-2%). However, these infants are at risk for later problems including fine and gross motor impairments, visuomotor integration, learning difficulties and attention deficit disorders (Wernovsky, Shillingford & Gaynor, 2005; Walker, Holland, Winlaw, Sherwood & Badawi, 2006). Congenital heart disease in itself is associated with neurodevelopmental impairment. One-third of the population that is operated for congenital heart disease have an underlying genetic disorder (Pierpont, Basson, Benson, Gelb, Giglia, Goldmuntz, McGee, Sable, Srivastava & Webb, 2007). A recent review by Latal (2016) described children with congenital heart disease that underwent open-heart surgery and found that they were at risk for neurodevelopmental impairments in all motor, learning, cognitive and language developmental domains. Adverse neurodevelopmental outcome related to congenital heart disease has often been attributed to the use of extracorporeal membrane oxygenation (ECMO) during surgery (Walker *et al.,* 2006). ECMO has been associated with hearing loss and neurodevelopmental impairment in 25-67% of survivors (Rasheed, Tindall, Cueny, Klein & Delaney-Black, 2001; Davis, Firmin, Manktelow, Goldman, Davis, Smith, Cassidy & Shekerdermian, 2004; Hanley, 2005).

Neonates with congenital diaphragmatic hernia and oesophageal atresia often require surgery. In survivors of oesophageal atresia, current studies show a mild to moderate reduction in mean IQ with a significantly increased rate of emotional and behavioural problems requiring special schooling (Bouman *et al.,* 1999).

In the majority of studies on anesthesia and surgery, it is not possible to distinguish the potential effects of comorbidities, clinical characteristics, and surgery from the effects of anesthesia (Wilder *et al.,* 2009). The rapid development of the fetal brain makes this patient group more vulnerable to anesthetic neurotoxicity. The growing number of fetal interventions requiring anesthesia make this a very important field of research inquiry (Andropoulos, 2018).

2.3.3 Intrauterine growth restriction

Intrauterine growth restriction is a major public health concern and, following preterm birth, the second greatest cause of perinatal mortality worldwide (Bernstein, Gabbe & Reed, 1996; Walker & Marlow, 2008). Various large follow-up studies have shown that intrauterine growth restriction is associated with significant neurodevelopmental impairment and outcomes (Alkalay, Graham & Pomerance, 1998; Strauss & Dietz, 1998; Wienerroither, Steiner, Tomaselli, Lobendanz & Thun-Hohenstein, 2001; Leitner, Mimouni Bloch, Sadeh, Neuderfer, Tikotzky, & Harel, 2002; Walker & Marlow, 2008; Baschat, 2011; Murray, Fernandes, Fazel, Kennedy, Villar & Stein, 2015).

There are three known types of intrauterine growth restrictions; symmetrical intrauterine growth restriction (hypoplastic small for date), asymmetrical intrauterine growth restriction (malnourished infants), and mixed intrauterine growth restriction. This classification is based on a number of clinical and anthropometric features (Table 2.1). Mixed intrauterine growth restriction is usually seen in middle to low income countries. Infants presenting with mixed intrauterine growth restriction have clinical features of both symmetrical and asymmetrical intrauterine growth restriction at birth (Sharma, Shastri & Sharma, 2016).

Table 2.1: Characteristics of symmetrical and asymmetrical intrauterine growth restrictions (Sharma *et al.,* 2016)

CHARACTERISTICS	SYMMETRICAL IUGR	ASYMMETRICAL IUGR
Period of insult	Earlier gestation	Later gestation
Incidence of total IUGR cases	20-30%	70-80%
Etiology	Genetic disorder or infection intrinsic to foetus	Utero-placental insufficiency
Antenatal scan, head circumference, Abdominal circumference, biparietal diameter and femur length	All are proportionally reduced	Abdominal circumference- decreased. Biparietal diameter, head circumference, and femur length- normal
Ponderal Index	Normal (>2)	Low (<2)
Postnatal anthropometry Weight, length and head circumference	Reductions in all parameters	Reduction in weight. Length and Head circumference- normal (Brain sparing growth)
Difference between head and chest circumference in term IUGR	Less than 3cm	More than 3cm
Features of malnutrition	Less pronounced	More pronounced
Prognosis	Poor	Good

IUGR: Intrauterine growth restriction

A systematic review conducted by Murray *et al.* (2015) found a correlation between children with intrauterine growth restriction, born <35 weeks of gestation and neurodevelopmental impairment. Children born with intrauterine growth restriction are impaired in the domains of cognitive and behavior development. Children born preterm or with evidence of fetal circulatory redistribution are at a higher risk for neurodevelopmental delay than children born with intrauterine growth restriction. A systematic review by Levine *et al.* (2014) reported a motor, cognitive and language delay up to three years, after diagnoses of intrauterine growth restriction. The neonatal risk factors associated with neurodevelopmental impairment after intrauterine growth restrictions include low birth weight fetal acidosis and placental villitis. Furthermore, preterm infants with intrauterine growth restriction scored lower on verbal IQ and full-scale IQ tests when tested at the age of five to eight years.

2.3.4 Steroids

Pharmacological doses of corticosteroids were previously widely used in neonatal intensive care units, resulting in short-term improvements in lung mechanics and oxygenation of the young neonate (Barrington & Finer, 1985). However, more recent studies have clarified that the only benefit of postnatal steroids is an acute improvement in gas exchange and lung mechanics (Barrington & Finer, 1998). Postnatal steroids have not improved long-term pulmonary health (Doyle & Davis, 2000; Barrington, 2001; Halliday, Ehrenkrantz & Doyle, 2010).

However, postnatal steroids have shown to be related to neurodevelopmental disabilities and movement disorders (O'Shea, Kothadia, Klinepeter, Goldstein, Jackson & Weaver, 1999; Linsell *et al.,* 2016). Postnatal steroids administered during the neonatal period is associated with a diagnosis of CP at about two years of age (Wilson-Costello, Walsh, Langer, Guillet, Laptook, Stoll, Shankaran, Finer, Van Meurs & Das, 2009; Linsell *et al.,* 2016). The early use of postnatal corticosteroids (within first eight days of life) was found to increase the incidence of CP (Halliday *et al.,* 2010), although later use (after the first seven days of life) was found to be non-significant (Halliday, Ehrenkranz & Doyle, 2009). In order to ensure maximum respiratory benefit with the lowest neurologic risk, Malaeb & Stonestreet (2014) suggested that firstly, gluco-corticoid therapy should be restricted to preterm infants born before 30 weeks' gestation with a high risk for developing bronchopulmonary dysplasia. Secondly, the first course of postnatal steroids should be considered at approximately day 14 of life (Malaeb & Stonestreet, 2014). At TCH, postnatal steroids are rarely used and when used, Minidex dosages are prescribed (personal correspondence with Dr. JCF du Preez, Neonatologist at Tygerberg Children's Hospital). The suggested dose is much lower than previously used in order to mimic physiological dosages: 0.05mg/kg/day for 10 days, followed by alternate dosage for six days (Yates & Newell, 2011).

Antenatal corticosteroid therapy has been recommended since 1994 for women at risk for delivery between 24 and 34 weeks' gestation, because it has shown a significant reduction in neonatal mortality and morbidity (Roberts & Dalziel, 2006). A systematic review by Sotiriadis *et al.* (2015) reported that one course of antenatal corticosteroids is associated with improved rates of intact survival and severe disability when compared to no steroids (Sotiriadis, Tsiami, Papatheodorou, Baschat, Sarafidis & Makrydimas, 2015). Multiple antenatal corticosteroid courses have demonstrated smaller head circumference

at birth (French, Hagan, Godfrey & Newnham, 1999; Kumar & Seshadri, 2005). At Tygerberg Hospital, the antenatal use of steroids is standard practice of care (personal correspondence with Dr. JCF du Preez, Neonatologist at TCH).

2.3.5 Necrotizing enterocolitis

Necrotizing enterocolitis is an acquired gastrointestinal disease and is considered a serious morbidity affecting ELBW infants and a 30% incidence of surgical intervention (Guthrie, Gordon, Thomas, Thorp, Peabody & Clark, 2003; Wadhawan, Oh, Hintz Blakely, Das, Bell, Saha, Laptook, Shankaran, Stoll & Walsh, 2014). Although necrotizing enterocolitis is not associated with developmental impairments, infants with necrotizing enterocolitis who require surgical intervention are at risk for growth delay and adverse neurodevelopmental outcomes (Xiong *et al.,* 2012). ELBW infants who develop necrotizing enterocolitis needing surgery represent a group on infants with extremely high morbidity and mortality, irrespective of surgical approach applied (Blakely, Lally, McDonald, Brown, Barnhart, Ricketts, Thompson, Scherer, Klein, Letton & Chwals, 2005; Rees, Eaton, Kiely, Wade, McHugh & Pierro, 2008).

Various large studies have shown an increased risk of poor growth and adverse neurodevelopmental outcomes in infants with surgical necrotizing enterocolitis (SurgNEC) in comparison to infants without SurgNEC (Tejani, Dobias, Nangia & Mahadevan, 1978; Whiteman, Wuethrich & Egan, 1985; Walsh, Kliegman & Hack, 1989; Pike, Brocklehurst, Jones, Kenyon, Salt, Taylor & Marlow, 2012; Shah, Meinzen-Derr, Gratton, Steichen, Donovan, Yolton, Alexander, Narendran & Schibler, 2012). Neonatal exposure to anesthesia has been associated with adverse neurodevelopmental outcomes and may be an influencing factor in the outcome of infants following SurgNEC (DiMaggio *et al.,* 2009; Wadhawan *et al.,* 2014).

2.3.6 Gender

In EPT infants, overall developmental impairment is more common in males (Johnson, Fawke, Hennessy, Rowell, Thomas, Wolke & Marlow, 2009; Kent, Wright & Abdel-Latif, 2012). Male infants are more likely to have lower movement assessment scores, autism spectrum disorders and CP (Limperopoulos, Bassan, Sullivan, Soul, Robertson, Moore, Ringer, Volpe & du Plessis, 2008; Beaino, Khoshnood, Kaminski, Marret, Pierrat, Vieux, Thiriez, Matis, Picaud, Rozé & Alberge, 2011; Leversen, Sommerfelt, Ronnestad, Kaaresen, Farstad, Skranes, Støen, Elgen, Rettedal, Eide & Irgens, 2011). Male infants

are more likely to be deaf (Hack *et al.,* 2000) and twice as likely to have language deficits (Wolke, Samara, Bracewell, Marlow & EPICure Study Group, 2008). Furthermore, male infants are more prone to sepsis, major surgery and IVH, factors resulting in poor nutrition, growth and neurological outcomes (Kent *et al.,* 2012; Frondas-Chauty, Simon, Branger, Gascoin, Flamant, Ancel, Darmaun & Rozé, 2014).

Female infants are more likely to have behavioural and emotional impairments. Adolescent females with a history of VLBW have more emotional and externalizing problems than their male peers (Dahl, Kaaresen, Tunby, Handegård, Kvernmo & Rønning, 2006).

2.4 Effect of perinatal factors on general movements (GMs)

Literature on the influence of perinatal factors on early neurodevelopment and GMs of the young high-risk infant is limited. Five papers (Zaheid-Cheick, Brévaut-Malaty, Busuttil, Monnier, Roussel & Gire, 2011; Hitzert, van der Laan, Roescher & Bos, 2012; Olsen *et al.,* 2015; Crowle *et al.,* 2017; Dostanic *et al.,* 2018) were found in an extensive and systematic search of six databases. A retrospective study by Dostanic *et al.* (2018) reported the effect of perinatal risk factors namely, assisted reproductive technologies, male gender, small for gestational age, twin pregnancy and Apgar score on the quality of GMs in a group of 89 twin pairs. The gestational age ranged from 24-38 weeks and birth weight between 670g-3820g. They found premature birth and a lower gestational age associated significantly with abnormal GMs at three to four months post-term age. However, the most common perinatal factors that have an effect on early neurodevelopment, for example, IVH and PVL were not included as risk factors.

A study by Zahed-Cheikh *et al.* (2011) investigated the correlation between antenatal, perinatal and postnatal risk factors and quality of GMs in 19 ELBW infants. GMAs were conducted at two time periods, the first between 30 and 40 weeks of age, and the second during the third month. No significant correlation was reported between GMs and antenatal factors including cesarean delivery, premature rupture of membranes and preterm labor. Gestational age correlated with abnormal GM trajectory during preterm GMAs. Fifty percent of infants with a gestational age <26 weeks presented with abnormal GMs. Fidgety movements correlated with the gestational age; 100% of infants with a gestational age of >26 weeks had normal fidgety movements, while 33% of infants with a gestational age of <26 weeks had absent fidgety movements. No correlation was found

between birth weight and hypotrophy on the brain ultrasound. Nosocomial infections correlated with preterm GM quality; 87.5% of infants with confirmed nosocomial infections had abnormal transitory GM trajectories. A correlation was observed between infants with patent ductus arteriosus and the quality of spontaneous preterm GMs. 87.5% of preterm infants with patent ductus arteriosus presented with altered GMs. Global trajectory of GMs correlated with an abnormal electroencephalogram (EEG), namely 100% of infants with an abnormal EEG had an abnormal global trajectory. Zahed-Cheikh *et al.* (2011) reported a correlation between MRI and fidgety movements; 66% of the infants with absent fidgety movements had an abnormal MRI.

A study by Olsen *et al.* (2015) assessed 149 VPT infants born at <30 weeks' gestation. GMs were recorded weekly from birth until 32 weeks PMA, and fortnightly until 38 weeks PMA, and term age. Extensive perinatal data was collected. Of the 669 GMAs, 551 were conducted at preterm age and 118 GMAs at term-equivalent age. Prior to term, 15% (n=82) of GMs were normal and 85% (n=469) were abnormal. The proportion of abnormal GMs decreased with increasing PMA. At corrected age for term, 30% (n=35) of GMs were normal. A univariable analysis showed that lower gestational age, bronchopulmonary dysplasia and infection were associated with an increased risk for abnormal GMs. However postnatal infection (necrotizing enterocolitis and/or sepsis) was the only variable that remained independently associated with abnormal preterm and term age GMs, when all variables were included in the regression model. All infants with significant brain injury on cranial ultrasound had abnormal GMs at preterm and term age assessments (Olsen *et al.,* 2015).

Preterm infants frequently require surgery after birth for either cardiac or congenital birth defects which can result in long term neurodevelopmental deficits, manifesting from one year of age until early adolescence (Walker, Badawi, Holland & Halliday, 2011). There was only one study (Crowle *et al.,* 2017) that conducted GMAs after surgery in 217 infants born at term age who had either cardiac or non-cardiac surgery during their first 30 days of life. GMs were assessed, following surgery, at term age and at three months corrected age. At term age, 54% (n= 117) of infants had a 'poor repertoire' GM pattern. At three months corrected age, the majority of infants (n = 190, 88%) had normal fidgety movements. There was no significant difference in the GMs between the cardiac and non-cardiac group at term and three months corrected age. The trajectory in the majority of

infants had normal GMs at the fidgety period (12-15 weeks post-term age), despite poor-repertoire GMs at term age.

Hitzert *et al.* (2012) conducted a study to investigate the effect of high-dose dexamethasone treatment administered to preterm infants at risk of bronchopulmonary dysplasia and the quality of GMs. Video recordings of infants (n=17) were made before high-dose dexamethasone treatment started, days 1, 2, and 7 following treatment, around term age, and at three months post term. The quality of GMs during the fidgety period improved in nine out of 13 initially abnormal infants. Infants with abnormal GMs during the fidgety period had severe bronchopulmonary dysplasia. At 12-36 months corrected age, 14 of the 15 surviving infants had a normal neurodevelopment. One infant had slightly delayed development. Shorter periods of mechanical ventilation and higher birth weight were associated with better GM trajectories.

2.5 Longitudinal general movement (GM) assessment

A trajectory of individual GMs (serial assessments) at various ages is needed for effective identification of normal and abnormal neurodevelopment. A GMA trajectory is necessary in order to understand the influence of perinatal factors on the early neurodevelopment of the preterm infant (Einspieler *et al*., 2004). Prediction of individual neurological development is based on GM trajectories (Einspieler & Prechtl, 2005). Six studies have used serial GMs from preterm, term till post-term age (Cioni *et al.,* 1997b; Bos *et al.,* 1997a; Bos, Martijn, Okken & Prechtl, 1998a; Ferrari *et al.,* 2002; Garcia *et al.,* 2004; Nakajima *et al.,* 2006). These studies included small sample sizes and demonstrated the necessity for research on GM trajectories in larger samples of VPT and EPT infants. The studies found that up to 60-70% of infants displayes abnormal GMs during the preterm age and 40-50% abnormal GMs during term age (Cioni *et al.,* 1997b; Bos *et al.,* 1997a; Bos, Martijn, Okken & Prechtl, 1998a; Ferrari *et al.,* 2002; Garcia *et al.,* 2004; Nakajima *et al.,* 2006). At three to four months corrected age the authors reported that 80-90% of infants had normal fidgety movements (Cioni *et al.,* 1997b; Bos *et al.,* 1997a; Bos *et al.,* 1998a; Ferrari *et al.,* 2002; Garcia *et al.,* 2004; Nakajima *et al.,* 2006).

2.6 Conclusion

There is an unacceptable discrepancy between high-income and low and middle income countries with respect to accessible support structures to assist high risk infants to reach their optimal developmental potential (WHO, 2012). Furthermore, systems to enable

prevention, detection and management of developmental difficulties during infancy and early childhood in low and middle income countries are lacking (WHO, 2012). These countries have a lower survival rate of premature or VLBW infants with a higher proportion of significant developmental difficulties (WHO, 2012). Furthermore, various perinatal factors such as IVH, PVL, lower gestational age and birth weight have been identified to influence the outcome of high risk preterm infants. The trajectory and understanding of GMs and neuro-developmental outcomes in high risk infants in low and middle income countries is inadequate. A descriptive study was conducted at TCH in Cape Town, South Africa with the intention that the results contribute to the relevance of GMA as a reliable assessment tool in preterm infants. The next chapter will describe the research question, study aim and objective as well as the methodology.

CHAPTER 3

METHODOLOGY

This chapter describes the research question, study objectives, study design, study population, sampling and instrumentation. The procedure, data analysis and ethical considerations are also described.

3.1 Research question

What is the quality of GM trajectories from birth until 12-14 weeks corrected age in preterm infants born before 33 weeks' gestation and weighing less than 1500g, admitted to the neonatal care units of TCH?

3.2 Study objectives

The primary objectives of the study were:

- To describe the quality of GM trajectories observed at the following four key time points: prior to term age (two time points), during term age and at 12-14 weeks corrected age in infants born before 33 weeks' gestation and weighing <1500g.
- To determine the association between the quality of GM trajectories observed prior to term age and at term age (two time points), compared to the quality of GMs observed at 12-14 weeks corrected age.

The secondary objective of the study was:

- To evaluate the association of the quality of GMs in infants who had experienced perinatal factors, such as IVH, PVL, necrotizing enterocolitis, intrauterine growth restriction, and infants who underwent a surgical procedure.

3.3 Study design

A longitudinal, prospective cohort design with repeated measures was conducted to answer the research question.

3.4 Study setting

The study was conducted at TCH. TCH is situated in the G Block of Tygerberg Hospital, which is the largest hospital in the Western Cape and second largest in South Africa. This hospital serves the immediate surrounding areas, providing primary and secondary health care to children, as well as tertiary care to all paediatric patients in Metro East, as well as

the Northern and Eastern rural districts of the Western Cape. Furthermore, Tygerberg Hospital acts as a teaching facility for the Stellenbosch University's Faculty of Medicine and Health Sciences. TCH primarily serves a diverse population dependent on the state of their health care needs. Furthermore, TCH is a tertiary referral centre for patients in the Metro East in the metropole of the Western Cape.

Admission and discharge criteria varies and TCH follows the guideline: *Neonatology: A guide to doctors working at Tygerberg Children's Hospital (2014).* The following information was obtained from this guideline. G1 and G2 neonatal wards both serve as admission wards: G2 admits all inborn infants (born at a gestational age <35 weeks and sick term born infants) from labour wards. G1 admits infants that requires admission from referral hospitals, infants younger than 10 days from G-ground ward, referrals from lower level wards, infants that need admission from puerperium wards as well as down referrals from NICU. In 2016, 850 infants born with a birth weight below 1500g were admitted to TCH. When infants are stable they are discharged to district or rural hospitals, including Khayelitsha-, Eersterivier-, Karl Bremer-, Stellenbosch-, Worcester- and Paarl Hospitals. These hospitals have different admission criteria depending on their availability of beds and staff. Some hospitals will admit infants with a weight of ≥1200g, while other hospitals will only admit infants if their weight is ≥1500g. TCH discharges infants when they are feeding independently, usually at a weight of 1800g and 34 weeks PMA.

High risk infants born at TCH are routinely followed up as outpatients at the Neonatal High Risk Clinic. The criteria for follow up are: preterm infants with a birth weight <1500g, infants who received cooling after birth and infants with known risk factors for delayed neurodevelopment, for example meningitis, severe neonatal jaundice, IVH grade III and IV. These infants are followed up at three months corrected age, 12 months corrected age and at three years of age. Infants with a birth weight <1000g have an additional appointment at term age. If a severe developmental delay is noted, more frequent follow up appointments are made. Infants with a known disability are followed up until placement at an appropriate school or facility (Personal correspondence with Dr JI van Zyl, neurodevelopmentalist, Neonatal High Risk Clinic, TCH).

3.5 Study population

The study population consisted of preterm infants weighing less than 1500g, born before 33 weeks gestational age and admitted to the neonatal wards of TBH.

3.5.1 Sample

Preterm infants born between the 1st of December 2017 and the 1st of May 2018 with a gestational age less than 33 weeks' and weighing <1500g. The infants selected for the sample were admitted to the neonatal wards of G1 and G2 at TCH.

3.5.2 Sampling method

A successive sampling method was used to select the study sample. Infants were recruited for the study after admission. The principal investigator (PI) visited the wards twice a week and identified eligible infants.

3.5.3 Inclusion criteria

The following inclusion criteria applied:

- Birth weight of <1500g. The reason for this weight limit is that only preterm infants weighing ≤1499g are being followed up after discharge at the Neonatal High Risk Clinic of TCH.
- Infants born before 33 weeks' gestation
- Participants with at least two GMAs
- Only participants residing from the following catchment areas of TCH will be included: the Northern Suburbs of Cape Town, the Cape Flats and surrounding towns within a 400km radius from TCH.

3.5.4 Exclusion criteria

The following exclusion criteria applied:

- Infants diagnosed with known syndromes or genetic/chromosomal defects (e.g. Down syndrome, Edwards syndrome).
- Infants with birth malformations of the central nervous system (e.g. myelomeningocele) or congenital disorders (e.g. arthrogryposis multiplex congenital, osteogenesis imperfecta congenital).
- Infants with microcephaly (≤ 3 percentile).
- Infants without written informed consent from parents or legal guardians.

3.5.5 Sample size

3.5.5.1 The initial pre hoc sample size

The hypothesis which was tested in this study was that there is a decrease in the percentage of abnormal GMs over time (PMA in weeks after birth). It was assumed, based on publications by Olsen *et al.* (2015) and Burger *et al*. (2011), that the proportion of abnormal GMs at the first assessment (birth to 33 weeks PMA) would be 95% and that this would decrease to 10% by the final assessment at 12-14 weeks corrected age. Using this assumption of a large change, only nine participants were needed at both time points to give 90% power for a McNemar's chi square test, at a significance level of 0.05. This study took into account at least ten covariates as confounders, making use of logistic regression methods to model the odds of changing from abnormal to normal over time, whilst adjusting for confounders. Therefore, a larger sample size would be necessary to accomplish this. A study by Olsen *et al.* (2015) used n=145 to accomplish similar objectives. This was a feasible number to use in the current study, since approximately 30-35 infants per month were expected to meet the inclusion criteria. During the data collection period of five months, the plan was for 160 infants to be enrolled, allowing for a 20% drop out rate after the first assessment.

3.5.5.2 Post hoc sample size calculation:

On completion of the five months' enrollment period 119 infants were recruited. GMAs were conducted on 81 of the infants at two time points. A *post hoc* power analysis was conducted using a two-sided McNemar'schi square test at a significance level of 0.05. It was determined that our sample size of 81 infants, assessed at two GM time points, achieved 100% power to detect an odds ratio of 0.053.

3.6 Instrumentation

Prechtl's method of the qualitative assessment of GMs was used to describe the integrity of the preterm infants' developing central nervous system. The psychometric properties of this method was described in Chapter 2, section 2.2.5.

3.7 Procedure

The following sections describe the ethical considerations, recruitment and the assessments of the infants. Figure 3.1 illustrates the timeline of the study procedure.

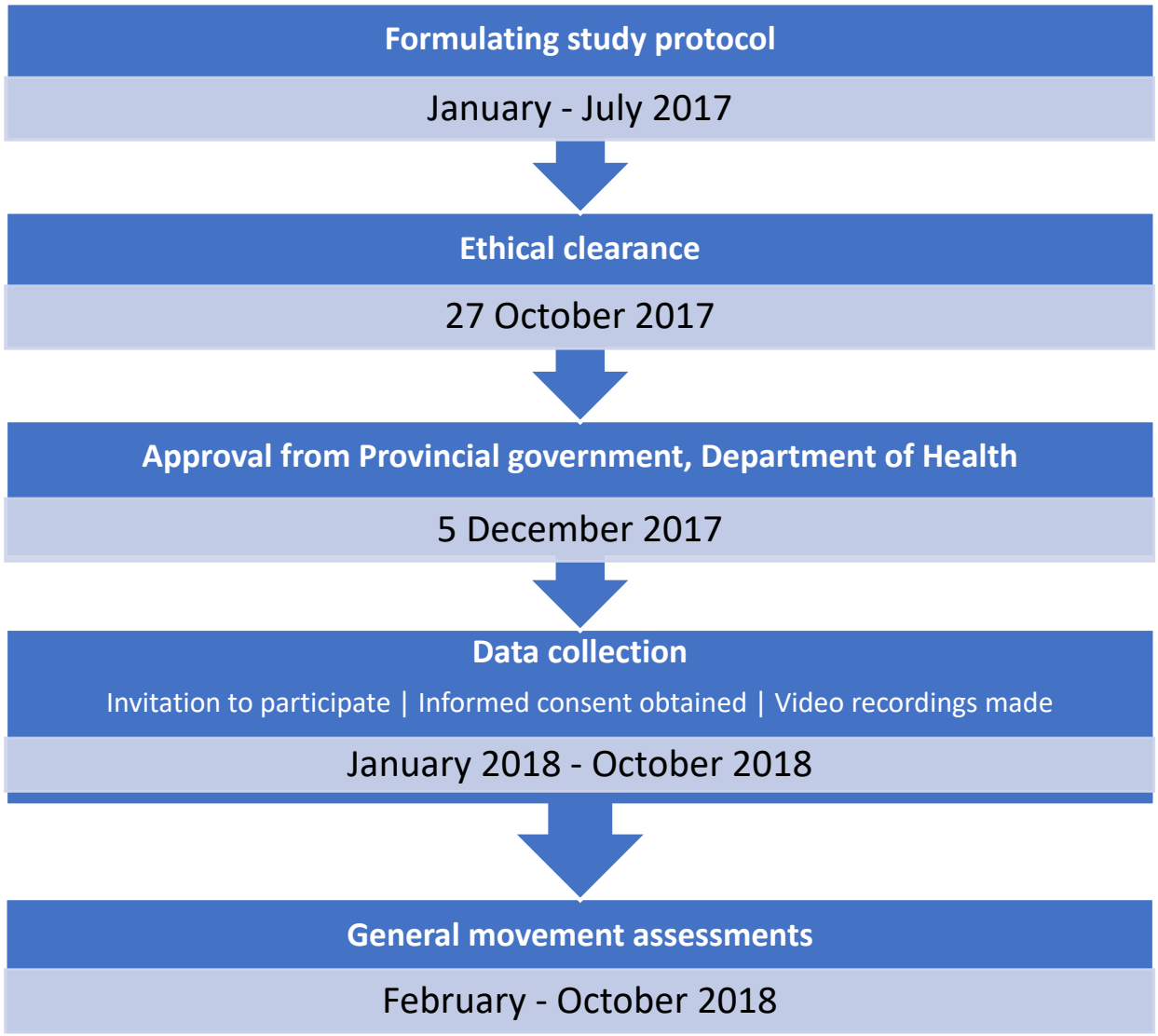

Figure 3.1 Timeline of the study procedures

3.7.1 Ethical considerations

Approval for conducting the study was obtained from the Committee of Human Research at Stellenbosch University (Addendum A). The study was conducted according to the internationally accepted ethical standards and guidelines as stipulated in the Declaration of Helsinki (2013) and South African Guideline for Good Clinical Practice (Moodley & Meyer, 2007). Permission was obtained from the Western Cape Department of Health and management of TCH, Karl Bremer-, Eersterivier- and Khayelitsha Hospitals (Addendum B).

The following ethical considerations were taken into account:

1. Confidentiality: The parent(s)/legal guardians were assured that information and data collected would be treated as confidential. The results will be published with participant anonymity.
2. Consent: Written informed consent were obtained from parents/legal guardians/caregivers of all included subjects (Addendum C).
3. Voluntary participation: Study participation of the parents and their infants were on a voluntary basis. If at any stage during the course of the study parents wished to withdraw, they were allowed to do so.
4. There were no foreseeable risks involved in this study. Any emergencies that could have occur during the video assessments would have been handled by medical practitioner or a registered nursing sister on duty in the neonatal wards or at Paediatric Outpatients.
5. Parents received no remuneration whilst their baby was hospitalized in TCH, Karl Bremer-, Eersterivier- or Khayelitsha Hospital. Parents did however, receive remuneration of R200.00 to cover transport costs upon follow up visits to the Neonatal High Risk Clinic, Paediatric Outpatients C3A, TCH (after discharge from Karl Bremer-, Eersterivier- and Khayelitsha Hospitals). Transport was arranged for mothers and infants that had to travel more than 50km (e.g. from Hermanus, Swellendam, Vredendal and Clanwilliam) to attend follow up visits.
6. Video recordings of GMAs were not destroyed since it formed part of a standard neurodevelopmental assessment procedure of all infants born premature, weighing ≤1499g and admitted to neonatal units at TCH. Video recordings were stored on external hard drives and locked in a secure cupboard in the office of Dr van Zyl in the Neonatal High Risk Clinic (Paediatric Outpatients, C3A).

3.7.2 Recruitment of infants

The PI was responsible for the recruitment of the study sample. The PI checked the admission books and the VERMONT network forms of the neonatal wards twice weekly and identified infants according to the inclusion and exclusion criteria.

3.7.3 Invitation to participate

Upon invitation to partake in the study, the PI explained the aims and study procedure and obtained informed consent from parent(s) or legal guardian(s) of the identified infants. Consent forms were available in Afrikaans and English (Addendum A). For parent(s) or

legal guardian(s) who did not understand Afrikaans or English, a Xhosa translator (Sister Limdelwa Plaatjies) was available to convey any questions, answers or uncertainty. Sister Plaatjies is trilingual and is fluent in Xhosa, English and Afrikaans. She is a qualified nursing sister (registered with the South African Nursing Council) with more than five years' experience as a trained research assistant in the field of GMAs. All participants were encouraged to contact the PI to discuss any queries with regards to the neurodevelopmental progress of their infant during the course of the study.

Upon receiving informed consent, each infant received an identification number and the following information was documented and entered into an Excel spreadsheet by the PI upon first assessment:

1) date of birth
2) birth weight in grams
3) gender
4) gestational age
5) parent/legal guardian contact number

3.7.4 Procedure for general movement assessments (GMAs)

The following sections describe the procedure of the data collection.

3.7.4.1 The different key age periods of general movement assessments (GMAs)

The following four key age periods were chosen for the serial video recordings of the infants:

Assessments of preterm GMs

i) One to two weeks after birth to 33 weeks PMA

ii) 34 – 37 weeks PMA

Assessment of writhing GMs

iii) Term age [GMAs were conducted at full term age (39 weeks 0 days - 40 weeks and 6 days PMA) and late term age (41 weeks 0 days - 41 weeks 6 days PMA)] (Spong, 2013).

Assessment of fidgety GMs

iv) 12-14 weeks corrected age.

3.7.4.2 Data collection and venue for the video recordings

The venue for video recordings depended on the age period during which the recording was made:

i) One to two weeks after birth to 33 weeks postmenstrual age (PMA)

Video recordings took place in the neonatal wards of G1, G2, G8 and J3 at TCH.

ii) 34 – 37 weeks PMA

Video recordings were made at TCH or at adjacent hospitals (Karl Bremer- Eersterivier- and Khayelitsha Hospitals) as some infants were transferred to hospitals closer to home. Infants discharged home were followed up at the Neonatal High Risk Clinic, Paediatric Outpatients C3A, TCH. The PI contacted the parents or legal guardians to schedule the video assessments. The parents or legal guardians received a remuneration of R200.00 to cover their transport costs to TCH.

iii) Term age

Video recordings were made at the following surrounding hospitals namely Karl Bremer-, Eersterivier- and Khayelitsha Hospitals. Infants discharged home were followed up at the Neonatal High Risk Clinic, Paediatric Outpatients C3A, TCH. The PI contacted the parents or legal guardians to schedule the video assessments. The parents or legal guardians received a remuneration of R200.00 to cover their transport costs to TCH.

iii) 12-14 weeks corrected age.

Video recordings were made during the first outpatient follow up visit at the Neonatal High Risk Clinic, Paediatric Outpatients C3A, TCH. The PI contacted and reminded the parents or legal guardians a week as well as 24 hours before the first outpatient appointment. Parents or legal guardians who failed to bring their infants on the day of the first outpatient appointment were contacted again and new appointments were scheduled for the following week.

3.7.4.3 Recording of general movements (GMs)

The first three GM trajectories were recorded by the PI. The final recording, at 12-14 weeks corrected age, was done by Dr. JI van Zyl during their outpatient follow up visit at the Neonatal High Risk Clinic. A light sensitive, high quality camera phone was used to record the spontaneous movement patterns onto cellphone memory. The angle used was directly from above. A digital camera was available for back up. Videos were immediately downloaded onto a laptop and saved on an external hard drive. Thereafter, all video recordings were deleted from the camera phone or digital camera.

3.7.4.4 The infants' position during video recordings

<u>One to two weeks after birth to 33 weeks postmenstrual age (PMA)</u>

Video recordings of the infants were done with the infant in the crib or incubator. The infant was placed in a supine position. The infant had sufficient room to move freely and was dressed lightly but warmly (thin nappy and vest) to allow free, unrestricted movement of the upper and lower limbs.

<u>34 – 37 weeks PMA</u>

Video recordings of the infants were done with the infant in the crib, incubator, on the mothers' bed in the Kangaroo Mother Care (KMC) ward or on the examination bed at the Neonatal High Risk Clinic. The infant was placed in a supine position. The infant had sufficient room to move freely and was dressed lightly but warmly (thin nappy and vest) to allow free, unrestricted movement of the upper and lower limbs.

<u>Term age & 12-14 weeks corrected age.</u>

For video recordings at term and post-term age, the infant was placed in supine position on a unicolor mattress on the floor or on the examination bed at the Neonatal High Risk Clinic. The infant had sufficient room to move freely and was dressed lightly (thin nappy and vest) to allow free, unrestricted movement of the upper and lower limbs and trunk. The temperature of the room was maintained at 22-24 degree Celsius to encourage the natural behaviour of the infant. Noise levels were kept to the minimum to reduce external factors that could distract the infant.

3.7.4.5 Behavioural state of the infant

Recordings made during the preterm age were taken during awake and asleep behavioural states of the infant (Einspieler & Prechtl, 2005). During term age and the

fidgety period (12-14 weeks corrected age), recordings were made with the infant in behavioural state 4 or active wakefulness according to Heinz Prechtl (Prechtl, 1997). This required the infant to be in a quiet alert state, with the absence of crying/fussing, while spontaneous movement patterns were observed. No pacifiers, toys or external stimulation of caregivers or the assessor were allowed. If the infant did start to cry or fuss during the video recording, the recording was temporarily paused, and the caregivers had the opportunity to console the infant before resuming the video recording.

3.7.4.6 Duration of the video recordings

The duration of the video recordings was dependent on the age period during which the infant is being recorded: during preterm age, 5-10 minutes of video recording was needed, independent of the behavioural state of the patient. From term age, 5 minutes of recording was sufficient (Einspieler & Prechtl, 2005).

3.7.4.7 Storage of the video recordings

The PI edited the video recordings to include 4-5 minutes of sufficient samples of GMs for each infant. The video recordings of each infant were downloaded and stored on a laptop. Back up files of video recordings were exported onto two external hard drives under each infant's identification number and name. The external hard drives were kept at separate secure locations namely, the office of Dr van Zyl in the Neonatal High Risk Clinic (Paediatric Outpatients, C3A) and at the Physiotherapy Division of Stellenbosch University.

3.7.4.8 Assessment of video recordings

The following assessors with advanced GMA certification from the General Movement Trust (http://general-movements-trust.info/5/home) were responsible for the assessments of GMs: Dr JCF du Preez, neonatologist at TCH; Dr JI van Zyl, neurodevelopmentalist at the Neonatal High Risk Clinic, Paediatric Outpatients C3A, TCH; Mrs A Crafford, paediatric physiotherapist; Mrs J Couper, paediatric occupational therapist and Mrs M Burger, senior lecturer at the Physiotherapy Division, Stellenbosch University.

3.7.5 Scoring of general movements (GMs)

GMs were independently scored by at least three qualified assessors mentioned in section 3.7.2.8. The assessors were blinded to the neonatal history of the infants. GMs

were assessed using Prechtl's method on the qualitative assessment of GMs and classified as either normal or abnormal according to the fluency, complexity and variability of the observed spontaneous movement patterns (Einspieler *et al.,* 2004). Individual scores were compared within the group. In the case of score discrepancies a discussion took place when five assessors were present and the videos were re-assessed. A consensus was reached if at least four of the five assessors gave the same score. If a consensus could not be reached, Prof Christa Einspieler, a licensed GM Trust tutor, made the final decision. Prof Christa Einspieler has been working with Prof Heinz Prechtl for the past 40 years and is a senior lecturer at the Centre for Physiological Medicine at the Medical University of Graz, Austria. The final scores were documented on an Excel spreadsheet next to the identification number of each infant.

3.7.5.1 From one to two weeks after birth (preterm age) until term age, general movements (GMs) were scored as follows:

i) Normal GMs: these movements are characterized by fluency and elegance, involving the whole body. They consist of variable patterns of flexion, extension and rotation of the limbs and rotation of the trunk and are complex in nature.

ii) Abnormal GMs were classified as:

- Poor-repertoire: movements that are lacking complexity and speed, amplitude and force, often observed as slower than normal GMs. Movements tend to be repetitive and monotonous.
- Cramped-synchronized: these movements are rigid in appearance, involving an almost simultaneous contraction and subsequent relaxation of all limbs and trunk muscles.
- Chaotic: movements that are large and abrupt in nature, involving all limbs and lacking fluency and elegance (Einspieler *et al*., 2004).

3.7.5.2 At 12-14 weeks corrected age (fidgety period) general movements (GMs) were scored as follows:

GMs during the fidgety period are divided into the following three categories:

i) Normal fidgety movements: these movements consist of circular movements of small amplitude, moderate speed and variable acceleration of the neck, trunk and limbs in all directions.

ii) Abnormal fidgety movements: these movements look like normal fidgety movements but their amplitude, speed and jerkiness are moderately or greatly exaggerated. Abnormal fidgety movements are extremely rare and their predictive value is low.

iii) Absent fidgety movements: fidgety movements are not observed, but other movements like wiggling-oscillating arm movements, swiping movements of the arms and kicking of the legs can still be observed (Einspieler *et al*., 2004).

3.7.6 Perinatal data

Perinatal information from the medical histories and neonatal course of the participating infants were collected and entered into an Excel spreadsheet.

This included:

- gestational age (weeks) [Foot length used to determine gestation] (Wyk & Smith, 2016),
- birth weight (grams),
- gender,
- type and duration of ventilation (invasive versus non-invasive),
- duration of oxygen via nasal cannula,
- length of hospitalization (days),
- the presence of IVH (IVH Grade III or IV),
- the presence of PVL (PVL Grade III or IV),
- necrotizing enterocolitis,
- postnatal corticosteroids,
- intrauterine growth restriction,
- anesthesia,
- culture gram-positive or negative sepsis,
- meningitis,
- exposure to the human immunodeficiency virus (HIV),
- multiple births

After the assessment of the GMs the association between these perinatal factors and GM scores were determined.

3.7.7 Data management

The collected data findings were entered into an Excel spreadsheet, coded and interpreted. For confidentiality purposes, a coding system were implemented whereby the infants' names on assessment documents were substituted by a code. These corresponding codes and records of infants' names were only available to the PI. The assessment data collected, consent forms and copies of video recordings were locked in a safe and secured place in the Physiotherapy Division, Stellenbosch University. Copies of video recordings were also stored on an external hard drive in the office of Dr JI van Zyl, at the Neonatal High Risk Clinic, Paediatric Outpatients C3A.

3.7.8 Xhosa translator

For parent(s) or legal guardian(s) who did not understand Afrikaans or English, a Xhosa translator (Sister Limdelwa Plaatjies) was available to convey any questions, answers or uncertainty. See section 3.7.3 for information on her qualifications.

3.7.9 Feedback to the parents

The parent/legal guardian were present during the video assessments. The infant's progress was discussed by Dr JI van Zyl upon their follow up at the High-Risk Clinic at TCH. Appropriate advice was given to the parent/legal guardians and the necessary referrals were made if any neurological impairments were identified. The parents of infants that failed to attend the 12-14-weeks corrected age follow-up visit were contacted and appointments were rescheduled.

3.8 Statistical analysis

The services of a statistician were utilized during the development of the protocol and the analysis of the results. STATA version 14 and IBM SPSS version 25 were used to analyze the data. A p-value <0.05 was considered statistically significant. The proportion of infants with normal and abnormal GMs over time was reported at each of the four key time points along with 95% confidence intervals. The change from one time point to the next in abnormal GMs was assessed by cross tabulation of normal and abnormal GMs at adjacent time points and also from the first time point to the last time point. McNemar's chi squared test was used to assess statistical significance in the change in proportions between two key time points. Logistic regression analysis adjusting for within-patient clustering over time was used to estimate the odds ratios and 95% confidence intervals

for the effects of time and the various confounding variables for the outcome of abnormal versus normal GMs. The potential confounders include:

- gestational age (weeks) [Foot length used to determine gestation]
- birth weight,
- gender,
- type and duration of ventilation (invasive and non-invasive),
- duration oxygen via nasal cannula,
- length of hospitalization,
- the presence of IVH (IVH Grade III or IV),
- the presence of PVL (PVL Grade III or IV),
- surgical necrotizing enterocolitis,
- postnatal corticosteroids,
- small for gestational age,
- any type of surgical procedure (and the use of anesthetic and analgesic agents),
- culture gram-positive or negative sepsis (including early onset - first 72 hours - as well as late onset sepsis),
- meningitis,
- exposure to HIV,
- multiple births.

The results will be presented in Chapter 4.

CHAPTER 4

RESULTS

In the following chapter the sample size, demographic profile, influence of perinatal factors and longitudinal GMA scores are presented. A significance level of 5% ($p<0.05$) was used as a guideline for determining significant differences. Numbers are rounded off to one decimal points.

4.1 Sample size

A total of 119 eligible infants were included in the study. All infants were recruited between December 2017 and May 2018 from the neonatal intensive care wards of TCH. A total of 300 GM video recordings were conducted over the four key time periods: 110 GMAs were done at birth to 33 weeks PMA, 47 GMAs at 34-37 weeks PMA, 55 GMAs at term age and 88 GMAs at 12-14 weeks corrected age. During the course of the study, 12 infants passed away of which nine were boys (Figure 4.1).

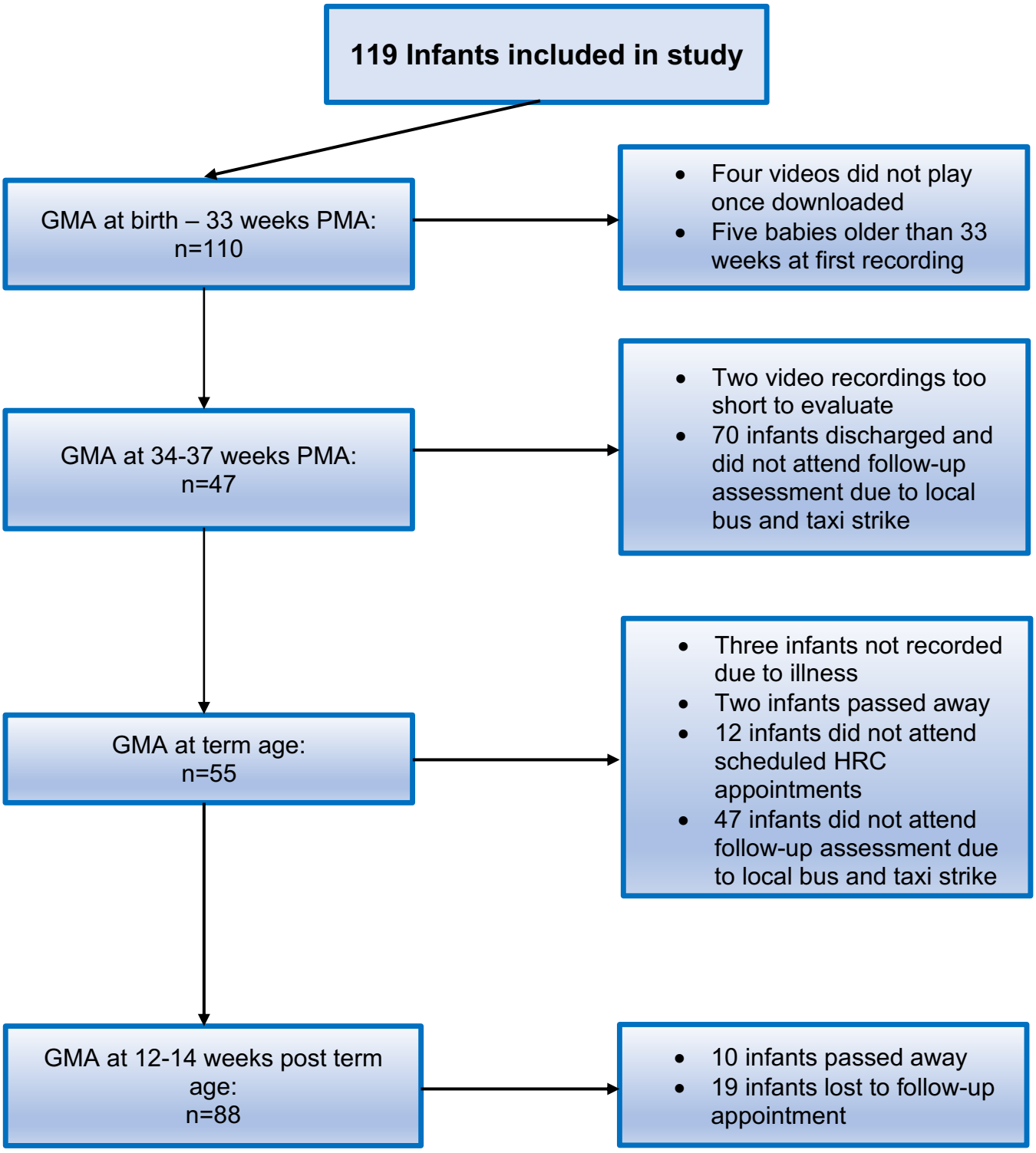

Figure 4.1 Study sample

4.2 Demographic profile of the sample

4.2.1 Gender, gestational age, birth weight and length of hospital stay

There were more female infants (53%) than male infants (47%) included in the study (Table 4.1). The distribution of the infants' gestational age, birth weight and length of hospital stay is shown in Figures 4.2, 4.3 and 4.4 respectively. The mean gestational age of the infants was 28.6 weeks and ranged from 24 to 33 weeks. The infants' birth weight ranged from 640g to 1455g, with a mean birth weight of 1048.2g. The mean length of hospital stay of the infants at TCH was 42.8 days, with a minimum of 5 and a maximum of 194 days.

Table 4.1 Characteristics of infants (n=119)

		Count	Percentage %
Gender	**Female**	63	52.9%
	Male	56	47.1%

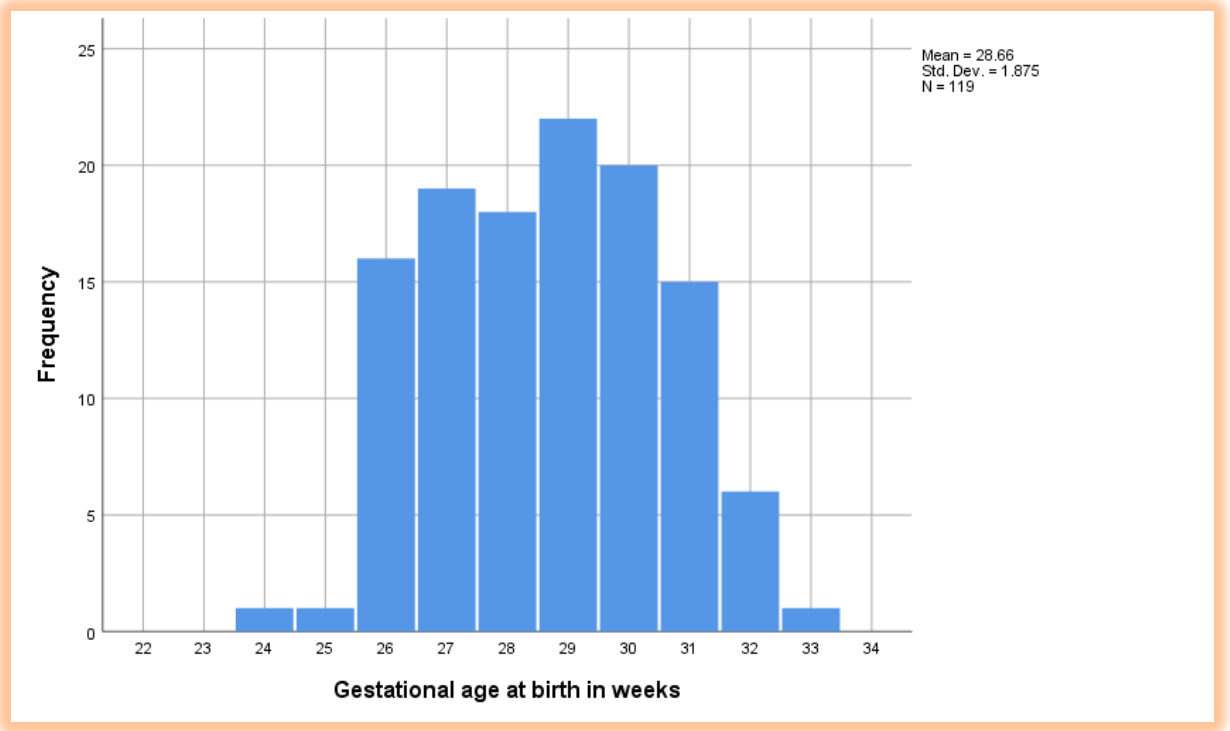

Figure 4.2 Frequency tabulation of gestational age of the infants (n=119)

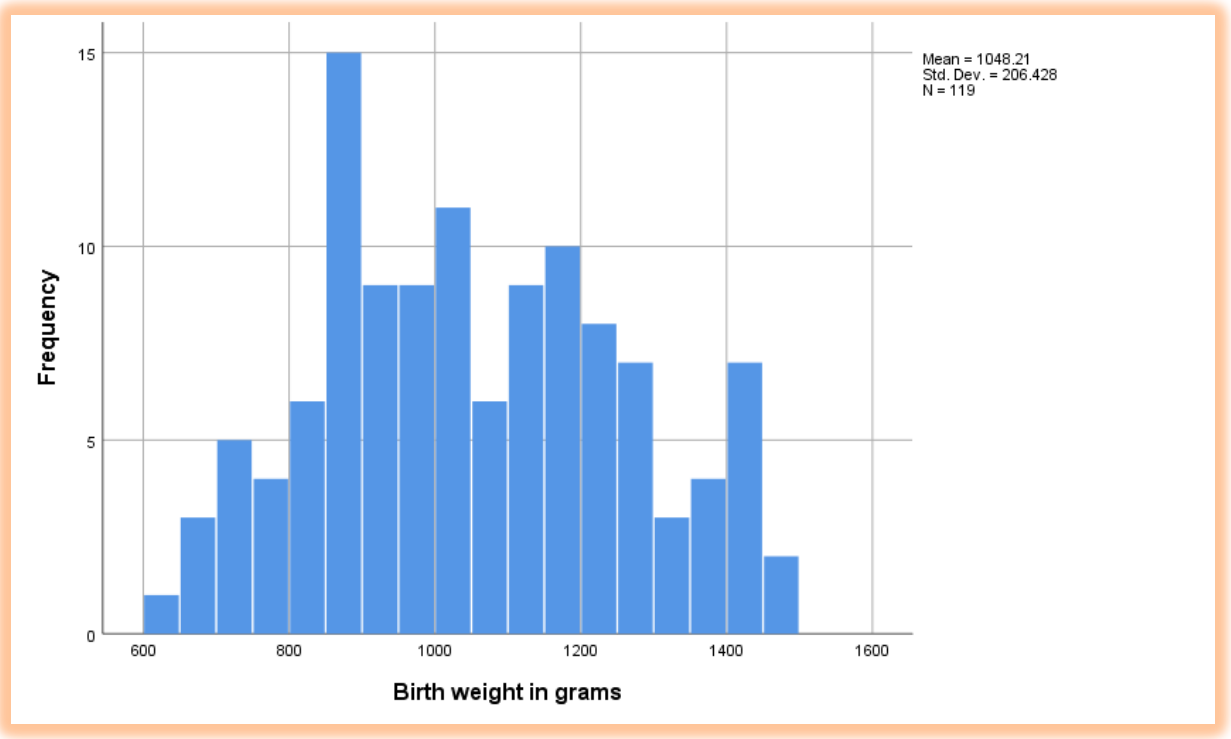

Figure 4.3 Frequency tabulation of birth weight of the infants (n=119)

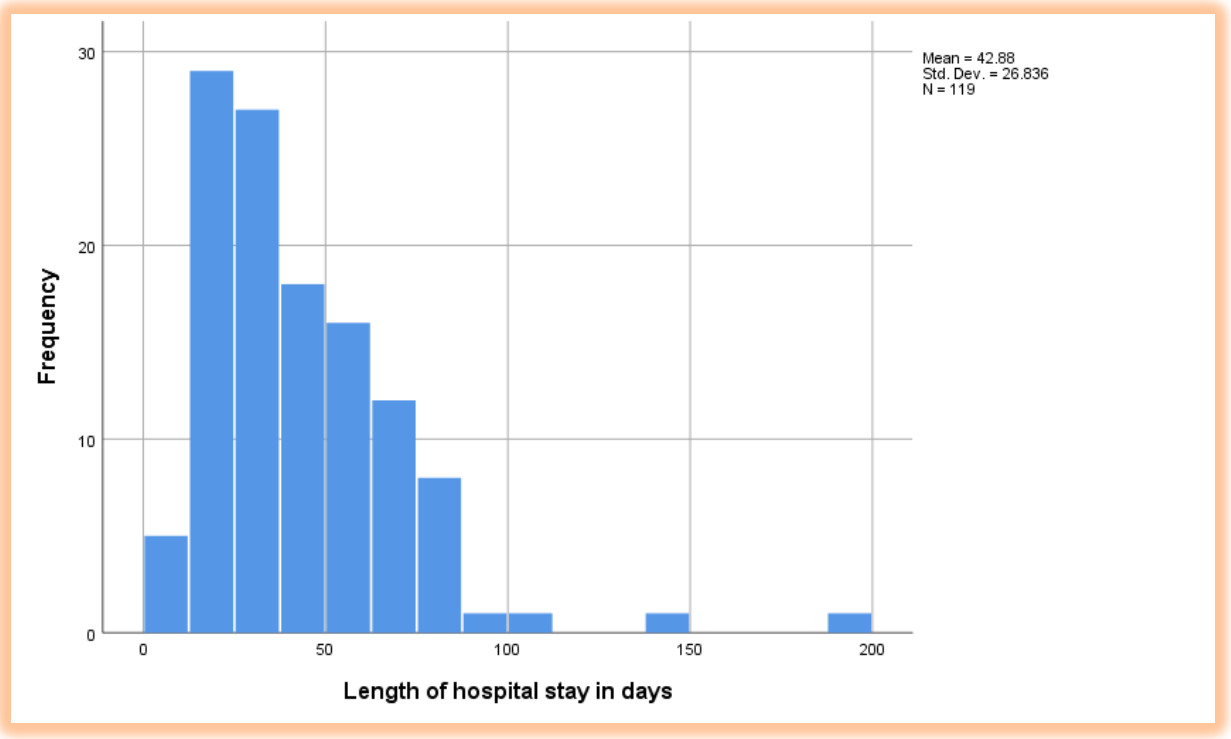

Figure 4.4 Frequency tabulation of the length of hospital stay of the infants (n=119)

4.2.2 Respiratory support

Nine (7.6%) of the 119 infants required invasive ventilation, while 109 (90.8%) required non-invasive ventilation (continuous positive airway pressure (CPAP) and high flow) and 91 infants (76.4%) required oxygen via nasal cannula (Table 4.2). In TCH is standard operating procedure to stabilize premature infants on CPAP non-invasive ventilation from birth if needed. If required, surfactant will be given via an endotracheal or nasogastric tube inserted through vocal cords into trachea. Thereafter they will continue to be supported by CPAP. Infants will only be intubated if they fail CPAP and need more support. Once their respiratory condition has improved on CPAP will they graduate onto high flow CPAP support or nasal cannula.

Table 4.2 Infants that received respiratory support

		Invasive ventilation	Non-invasive ventilation	Oxygen via nasal cannula
Count	**No**	110	10	28
	Yes	9	109	91

The duration of respiratory support in days is shown in Figures 4.5, 4.6 and 4.7 respectively. Of infants that received invasive ventilation, the duration ranged between one and 30 days. Infants that received non-invasive ventilation had a duration of a minimum of one and a maximum of 80 days. In the group of infants that had nasal oxygen, the duration ranged between one and 77 days. These infants usually received 21% O_2 at a flow of 2l/min.

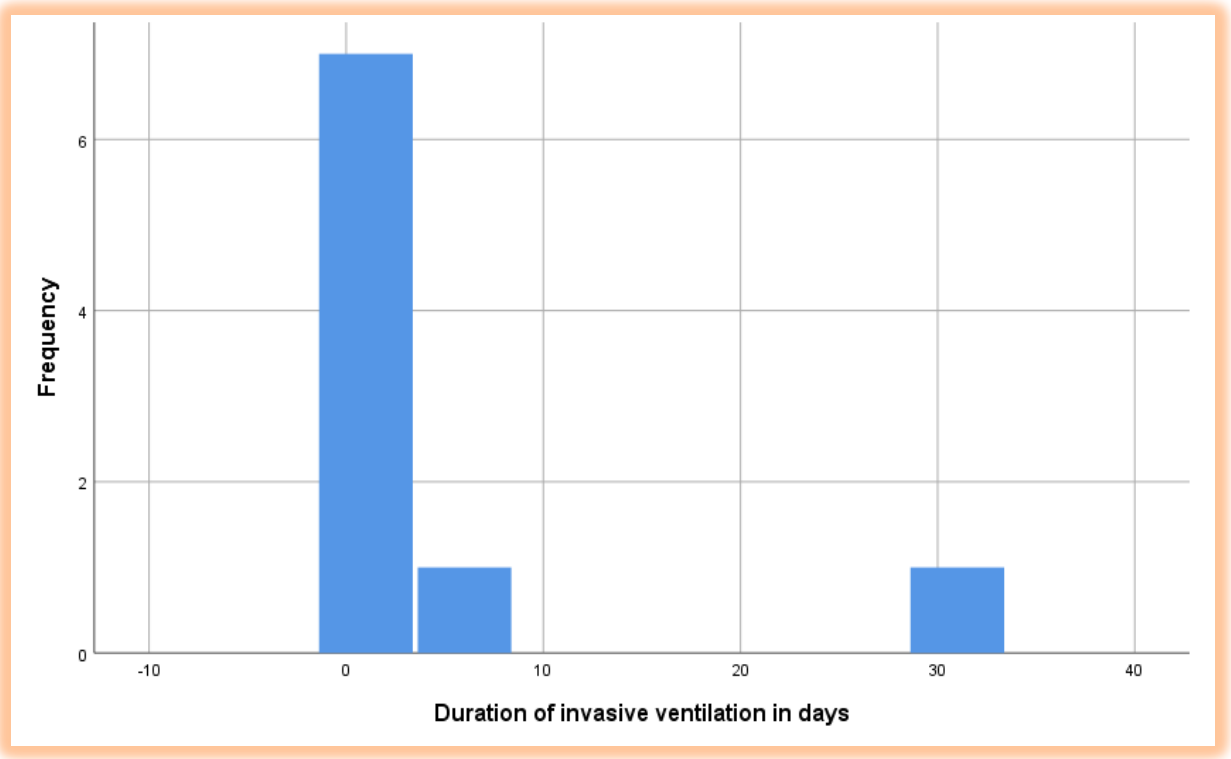

Figure 4.5 Duration of invasive ventilation administered to infants (n=9)

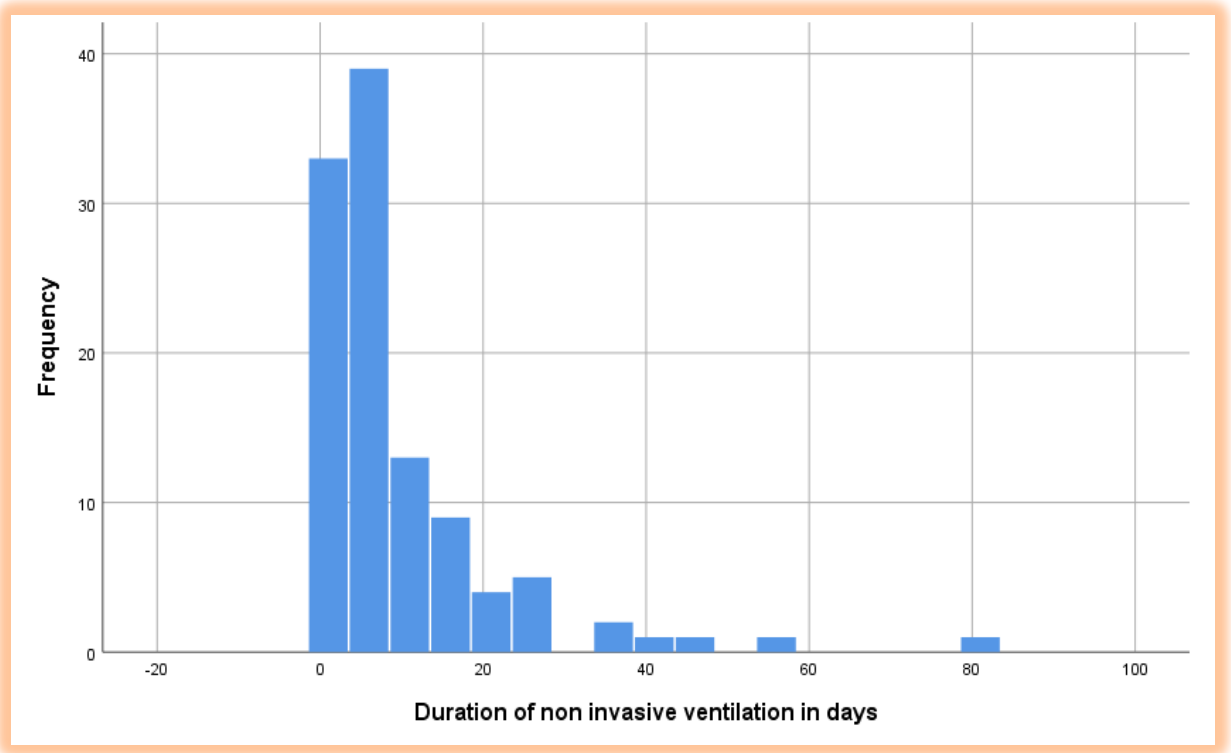

Figure 4.6 Duration of non-invasive ventilation administered to infants (n=109)

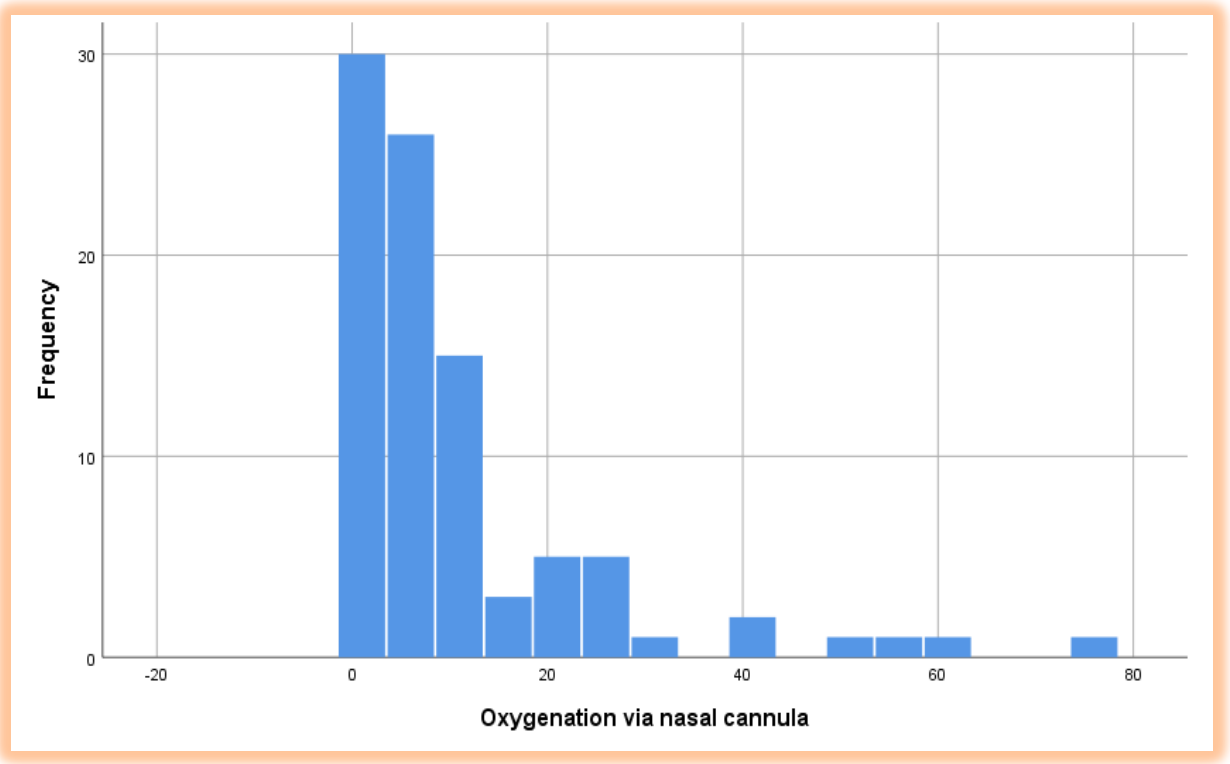

Figure 4.7 Duration of oxygen via nasal cannula administered to infants (n=91)

4.2.3 Perinatal factors

The most common perinatal factors are depicted in Table 4.3. Four infants had IVH grade III and one infant had IVH grade IV on cranial ultrasound. PVL was seen on cranial ultrasound in six (5%) infants. Necrotizing enterocolitis was diagnosed in 16 (13.4%) infants and intrauterine growth restriction was diagnosed in 23 (19.3%) infants. Nine (7.6%) infants were exposed to anesthesia of which only one infant had more than one exposure. Sepsis was diagnosed in 37 (31.1%) infants and no infants had meningitis. A total of 27 (22.7%) infants were exposed to HIV at birth. Of the included infants, 20 (16.8%) were part of a twin pair. Antenatal steroids were given to 93 (78.2%) mothers.

Table 4.3 Perinatal risk factors of infants (n=119)

		Count	Percentage %
IVH grade III	**No**	115	96.6%
	Yes	4	3.4%
IVH grade IV	**No**	118	99.2%
	Yes	1	0.8%
PVL	**No**	113	95.0%
	Yes	6	5.0%
NEC	**No**	103	86.6%
	Yes	16	13.4%
Antenatal steroids	**No**	26	21.8%
	Yes	93	78.2%
IUGR	**No**	96	80.7%
	Yes	23	19.3%
Anesthesia	**No**	110	92.4%
	Yes	9	7.6%
Sepsis	**No**	82	68.9%
	Yes	37	31.1%
Meningitis	**No**	119	100.0%
HIV exposure	**No**	92	77.3%
	Yes	27	22.7%
Twin births	**No**	99	83.2%
	Yes	20	16.8%

IVH: Intraventricular heamorrhage; PVL: Periventricular leukomalacia; NEC: Necrotizing enterocolitis; HIV: Human Immunodeficiency Virus

4.3 General movement assessment (GMA) score results

The GMA score results of the four different key time points are shown in Table 4.4. During the first time point (from birth to 33 weeks PMA) 110 infants were assessed, four scored normal, 105 poor-repertoire and one infant scored cramped-synchronized. During the second time point (34-37 weeks PMA) 47 infants were assessed. Five scored normal, 40 poor-repertoire and two infants scored cramped-synchronized. At the third time point (term age) 55 GMAs were done, none had a normal score, 54 scored poor-repertoire and one infant scored cramped-synchronized. During the final time point (12-14 weeks corrected age) 88 GMAs were conducted, 82 had normal fidgety movements, six had absent fidgety movements and none had abnormal fidgety movements.

Table 4.4 GMA results at key time points

		Count	Percentage %
GMA: birth to 33 weeks PMA (n=109)	**Normal**	4	3.6%
	Poor-repertoire	105	95.5%
	Cramped-synchronized	1	0.9%
GMA: 34-37 weeks PMA (n=47)	**Normal**	5	10.6%
	Poor-repertoire	40	85.1%
	Cramped-synchronized	2	4.3%
GMA: term age (n=55)	**Poor-repertoire**	54	98.2%
	Cramped-synchronized	1	1.8%
	Normal	0	0%
GMA: 12-14 weeks corrected age (n=88)	**Normal fidgety**	82	93.2%
	Absent fidgety	6	6.8%

GMA: General movement assessment; PMA: Postmenstrual age

The proportion of infants that scored abnormal during the different time points can be seen in Table 4.5. The proportion of abnormal scores at the first assessment (birth to 33 weeks PMA) was 96% of infants. At 34-37 weeks PMA, 89% of infants scored abnormal. All infants scored abnormal at term age and 7% of infants scored abnormal at 12-14 weeks corrected age. The proportion of infants with an abnormal score thus decreased with 90% from baseline (birth-33 weeks postmenstrual age) to final assessment at 12-14 weeks corrected age.

Table 4.5 Proportions of abnormality

GMA time point	Proportion abnormal	95% Confidence interval
Birth-33 weeks PMA (n=106)	96%	0.90-0.99
34-37 weeks PMA (n=42)	89%	0.77-0.96
Term age (n=55)	100%	N/A
12-14 weeks corrected age (n=6)	6%	0.03-0.14

PMA: Postmenstrual age; GMA: General movement assessment

4.4 Association between GMAs at key time points

McNemar's chi squared test was used to assess the statistical significance in the change in proportions over time between two GMA time points.

4.4.1 Birth to 33 weeks postmenstrual age (PMA) GMAs in association with 34-37 weeks postmenstrual age (PMA) GMAs

As seen in Table 4.6, a total of 45 infants were assessed at both birth to 33 weeks PMA and 33-37 weeks PMA to term age. Only one infant scored normal at the birth to 33 weeks PMA and remained normal at 34-37 weeks PMA. One infant that scored normal at birth to 33 weeks PMA deteriorated to abnormal at 34-37 weeks PMA. Three infants that scored abnormal at birth to 33 weeks PMA improved to a normal score at 34-37 weeks PMA and 40 infants that scored abnormal at birth to 33 weeks PMA remained abnormal at 34-37 weeks PMA.

Table 4.6 Association between GMAs at birth to 33 weeks postmenstrual age (PMA) and GMAs at 34-37 weeks postmenstrual age (PMA).

		GMA: 34-37 weeks PMA		Total
		Normal	Abnormal	
GMA: birth to 33 weeks PMA	Normal	1	1	2
	Abnormal	3	40	43
Total		4	41	45

PMA: Postmenstrual age; GMA: General movement assessment

4.4.2 34-37 weeks postmenstrual age (PMA) GMAs in association with GMAs at term age

GMAs were conducted on a total of 26 infants at both 34-37 weeks PMA to and at term age (Table 4.7). None of the infants had a normal score at term age. One infant that had a normal score at 34-37 weeks PMA scored abnormal at term age. The other 25 infants' GMA scores remained abnormal for both time points.

Table 4.7 Association between GMA scores at 34-37 weeks postmenstrual age (PMA) and GMA at term age

		GMA at term age	Total
		Abnormal	
GMA: 34-37 weeks PMA	**Normal**	1	1
	Abnormal	25	25
Total		26	26

PMA: Postmenstrual age; GMA: General movement assessment

4.4.3 Term age in association with 12-14 weeks corrected age GMAs

None of the infants had a normal GMA score at term age and therefore it was not possible to conduct a cross tabulation to analyze the association between GMAs at term age and GMAs at 12-14 weeks corrected age.

4.4.4 Birth to 33 weeks postmenstrual age (PMA) GMAs in association with 12-14 weeks corrected age GMAs

The association between the first (birth to 33 weeks PMA) and final (12-14 weeks corrected age) GMA time points can be seen in Table 4.8. A total of 81 infants were assessed at both birth to 33 weeks PMA and 12-14 weeks corrected age. Three infants that had a normal score at birth to 33 weeks PMA, remained normal throughout the study. A large proportion of infants (n=73) that had an abnormal score at the first assessment (birth to 33 weeks PMA), improved to a normal score at the final assessment (12-14 weeks corrected age). There were five infants with an abnormal score at the first assessment that remained abnormal throughout the study.

Table 4.8 Association between GMAs at birth to 33 weeks postmenstrual age (PMA) and 12-14 weeks corrected age

		GMA: 12-14 weeks corrected age		Total
		Normal	**Abnormal** (Absent fidgety movements)	
GMA: Birth to 33 weeks PMA	**Normal**	3	0	3
	Abnormal	73	5	78
Total		76	5	81

PMA: Postmenstrual age; GMA: General movement assessment

4.5 Association between perinatal factors and general movement (GM) outcomes

The association between perinatal risk factors and GMs were assessed using a logistic regression model. On univariate analysis, lower birth weight (p=0.043), gestational age at birth (p=0.017), IVH gr IV (p<0.001) and time (PMA in weeks) (p<0.001) were all associated with increased odds for abnormal GMs (Table 4.9). All models were adjusted for repeated measures by clustering using robust standard errors.

Table 4.9 Univariate analysis of perinatal risk factors for abnormal GMs

	Odds ratio (95% CI)	z score	p > | z |
Time	0.098 (0.04-0.25)	-4.78	0.000
BW in grams	0.99 (0.998-0.999)	-2.03	0.043
Gender	1.27 (0.91-1.78)	1.39	0.164
HIV exposure	1.48 (0.95-2.31)	1.72	0.086
GA at birth	0.91 (0.85-0.98)	-2.39	0.017
Length of hospital stay	1.01 (0.99-1.01)	1.61	0.108
Non-invasive ventilation	1.32 (0.87-2.01)	1.32	0.187
Invasive ventilation	0.68 (0.35-1.36)	-1.08	0.281
Nasal oxygenation	1.01 (0.99-1.02)	1.19	0.236
IVH gr III	1.02 (0.70-1.47)	0.09	0.930
IVH gr IV	0.43 (0.37-0.51)	-9.54	0.000
PVL	1.09 (0.48-2.50)	0.21	0.834
NEC	1.35 (0.86-2.12)	1.31	0.189
IUGR	1.18 (0.79-1.76)	0.81	0.421
Antenatal steroids	1.13 (0.77-1.65)	0.60	0.546
Anesthesia	1.42 (0.86-2.35)	1.35	0.176
Sepsis	1.09 (0.78-1.53)	0.52	0.600
Twin births	1.39 (0.92-2.09)	0.59	0.111

BW: Birth weight; HIV: Human Immunodeficiency Virus; GA: Gestational age; IVH: Intraventricular hemorrhage; PVL: Periventricular leukomalacia; NEC: Necrotizing enterocolitis; IUGR: Intrauterine growth restriction; Time=PMA in weeks

The following variables were included in a multivariable analysis: lower birth weight (p=0.043), gestational age at birth (p=0.017), IVH gr IV (p<0.001), time (p<0.001) and HIV exposure (p=0.086). Since birth weight and gestational age were highly correlated and thus collinear, gestational age was dropped from the final model. Birth weight (p=0.046) and time (PMA in weeks) (p<0.001) were the only variables that remained significantly associated with abnormal GMs after adjustment for confounding (Table 4.9).

Table 4.10 Multivariate analysis of perinatal risk factors for abnormal GMs

	Odds ratio (95% CI)	**z score**	**p > | z |**
BW in grams	0.998 (0.997-0.999)	-1.99	0.046
Time (PMA in weeks)	0.098 (0.04-0.25)	-4.88	0.000

BW: Birth weight; CI: Confidence interval; PMA: Postmenstrual age

CHAPTER 5

DISCUSSION

5.1 Introduction

The quality of spontaneous movement patterns observed in infants reflects the integrity of the young nervous system and serves as a predictor for later neurological outcomes (Einspieler, 2005). Although the assessment of GMs has been utilized for over 20 years, to date, only one study on the predictive value of GMs has been done in a South African setting (Burger *et al.,* 2011). Furthermore, there are only six studies globally that reported on preterm and post-term GMA trajectories at the following three key time points: preterm, term age (37-42 weeks PMA) and at 12-15 weeks post-term age (Cioni *et al.,*1997b; Bos *et al.,* 1997a; Bos *et al.,* 1998a; Ferrari *et al.,* 2002; Garcia *et al.,* 2004; Nakajima *et al.,* 2006).

The purpose of this study was to describe the quality of GM trajectories at four key time points from early preterm age till 12-14 weeks corrected age in VLBW and ELBW infants admitted to a tertiary hospital in South Africa. Furthermore, the study aimed to evaluate the association between certain perinatal risk factors and the quality of GMs. A discussion of the results of the current study, and a comparison to studies that investigated similar topics, will be presented in this chapter.

5.2 The quality of general movement (GM) trajectories

5.2.1 Outcome of preterm general movement assessments (GMAs)

In the current study, the majority of infants displayed abnormal GMs during preterm assessments: 96% of infants at birth to 33 weeks PMA and 89% of infants at 34-37 weeks PMA (Table 4.5). These results are consistent with the findings from previous studies that reported on at least two GMAs prior to term age of VLBW and ELBW infants (Bos *et al.,* 1997c; de Vries *et al.,* 2008; de Vries *et al.,* 2010; Olsen *et al.,* 2015).

Olsen *et al.* (2015) included 149 VPT infants and reported that only abnormal GMs were recorded between 25-28 weeks PMA. The proportion of normal GMAs increased from 13% at 29 and 34 weeks PMA respectively, to 20% at 38 weeks PMA (Olsen *et al.,* 2015). Similar results were reported by de Vries *et al.* (2008). They assessed GM trajectories on five occasions during the first 14 days of life in 19 ELBW infants (gestational age varying

between 25-31.1 weeks). Almost all GMs were found to be abnormal, of which poor-repertoire was most often observed. A larger study by de Vries *et al.* (2010) included 45 ELBW infants with a gestational age range of 25-32 weeks PMA. They evaluated GM trajectories during the first 10 days of early preterm life and reported that the majority of infants displayed abnormal GMs at the four assessment time points: namely 93%, 78%, 74% and 66%. Bos *et al*. (1997c) included 19 small-for-gestational age infants of whom the majority (79%) displayed abnormal GM trajectories during preterm.

Studies that reported on preterm GMA trajectories (Bos *et al.,* 1997c; Bos *et al.* 1998a; de Vries *et al.,* 2008; de Vries *et al.,* 2010; Olsen *et al.,* 2015) and those that conducted one GMA prior to term age (Ferrari *et al.,* 2002; Garcia, Gherpelli & Leone, 2004; Zahed-Cheick *et al.,* 2011) concluded that infants mostly displayed abnormal preterm GMs. Olsen *et al.* (2015) included a large sample size (n=149), while all the other studies included much smaller sample sizes. Bos *et al.* (1997c), Zahed-Cheick *et al.* (2011) and de Vries *et al.* (2008) included 19 infants, Bos *et al.* (1998a) included 27 infants and de Vries *et al.* (2010) included 45 infants. Garcia *et al.* (2004) assessed 33 infants during preterm age.

The consistent findings in this study and the above-mentioned studies of abnormal GM trajectories during the preterm age can be explained by the neurophysiological characteristics of the young nervous system. GMs are a major expression of the developing brain (Hadders-Algra*,* 2018). Most of the brain lesions in preterm infants occur in the periventricular white matter. Severe white matter lesions are strongly associated with abnormal GM trajectories as well as abnormal neurodevelopmental outcomes (Hadders-Algra, 2018). Spittle *et al.* (2008) reported that mild white matter injury is very common in preterm and infants with transient abnormal GM trajectories. Abnormal GM trajectory followed by normal GMs at 12-14 weeks corrected age, displayed mild white matter injuries. They found that all preterm infants with normal GM trajectories had no or mild white matter abnormality on MRI. However, infants with transient GM abnormalities had mild white matter injuries (Spittle *et al.,* 2008). The location of white matter injuries in the preterm brain may also be of importance. The echodensities in the frontal white matter on cranial ultrasound, which resolved before the 14th day of life, did not seem to have any impact on the quality of GM trajectories. There was, however a strong correlation between the duration of echodensities in the parieto-occipital white matter and abnormal GM trajectories (Bos *et al.,* 1998a). Abnormal GMs displayed during the

preterm age have also been related to the susceptibility of the infant to acute perinatal factors as a result of infant immaturity and instability during this time (Bos *et al.,* 1997c; Zahed-Cheick *et al.,* 2011).

5.2.2 Outcome of term age general movement assessments (GMAs)

No infants displayed normal GMs at term age assessments (Table 4.4). Of the 26 infants assessed at both birth to 33 weeks PMA and at term age, only one infant transitioned from a normal GM trajectory at preterm assessment to abnormal at term age. No significant clinical events were identified to cause this infant's transition. All other infants (n=25) were abnormal prior to term age (Table 4.7). This increase proportion of abnormal GMs from preterm (96%; 89%) to term age (100%) differs from what was reported in previous studies that evaluated GMs from preterm to term age (Bos *et al.,* 1997c; Garcia *et al.,* 2004; Zahed-Cheick *et al.,* 2011; Olsen *et al.,* 2015). A decreased proportion of abnormal GMs from preterm (79%) to term age (47%) in a total of 19 preterm infants was reported by Bos *et al.* (1997c). Similarly, Garcia *et al.* (2004) reported 60% abnormal GM scores at preterm age and a slightly lower 56% at term age in a total of 39 preterm infants. Olsen *et al.* (2015) reported a lower proportion of abnormal GMs at term age (70%) than at preterm age (85%).

It is unclear why all the infants assessed at term age (n=55) in the current study displayed abnormal GMs. A possible explanation may be that the birth weight of 85% of the infants followed up at term age were below 1200g. Furthermore, 73% (40/55) of infants had a gestational age <29 weeks PMA. A large prospective study investigating the risk factors associated with GM quality in 618 preterm infants found that lower gestational age and birth weight were significantly associated with abnormal GMs at term age (Ma, Meng, Chen, Yi, Wang & Cao, 2018).

The large proportion (98.2%) of poor-repertoire GMs during term age in the current study (Table 4.4) is a common finding. In a study by Olsen *et al.* (2015) 83 out of 118 infants assessed at term age had an abnormal GMs score, of which 98% had poor-repertoire and 2% cramped-synchronized scores (Olsen *et al.,* 2015).

In the current study, one infant displayed cramped-synchronized movements from birth to 33 weeks PMA and two infants at the 34-37 weeks PMA assessments. Cramped-synchronized movements are a strong indicator of a more severe white matter lesion

(Spittle *et al.,* 2008). Despite several attempts to remind the parents of the importance of the infants' follow-up visits, all three infants were lost to follow before their term age GMA. Consistent cramped-synchronized movements during preterm and term age is a specific sign for the development of severe spastic CP (Einspieler *et al.,* 2004). Previous studies have reported varying outcomes for transient cramped-synchronized GMs, including normal outcomes, CP and mild motor impairment (Cioni *et al.,* 1997b; Ferrari *et al.,* 2002; Mutlu, Livanelioglu & Korkmaz, 2010).

5.2.3 Outcome of general movement assessments (GMAs) at 12-14 weeks corrected age

None of the infants in the current study displayed abnormal fidgety movements at 12-14 weeks corrected age GMAs. Abnormal fidgety movements are extremely rare and of low predictive value (Prechtl *et al.,* 1997; Einspieler *et al.,* 2004). In the current study, 7% of infants had absent fidgety movements at 12-14 weeks corrected age. This is lower than the percentage of infants that displayed absent movements (9%) in a previous study conducted at TCH in 115 preterm infants with a birth weight of ≤ 1250g (Burger *et al.,* 2007). Other studies that included both high- and low risk infants reported higher percentages of infants with absent fidgety movements, namely 13% (Sharp, Coenen & Amery, 2018), 22% (Spittle *et al*., 2013), 25% (Spittle *et al.,* 2008), 18% (Adde, Rygg, Lossius, Øberg & Støen, 2007) and 11% (Ivanov, Shukerski & Chepisheva, 2005). None of these studies (Ivanov *et al.,* 2005; Adde *et al.,* 2007; Burger *et al.,* 2007; Sharp *et al.,* 2018) reported abnormal fidgety movements. Two previous studies (Prechtl, 1997; Garcia *et al.,* 2004) reported the following percentages of abnormal and normal fidgety movements: 12% abnormal and 35% absent fidgety movements (Garcia *et al.,* 2004), and 12% abnormal and 34% absent fidgety movements (Prechtl, 1997).

In the current study, 82 infants were assessed at both baseline (birth to 33 weeks PMA) and at 12-14 weeks corrected age. There was a significant decrease in the proportion of infants that displayed abnormal GMs, from 73 infants at the first assessment (birth to 33 weeks PMA) to five infants at the final assessment (12-14 weeks corrected age) (See Table 4.8). This is consistent with previous published findings that reported a significant decline in the proportion of abnormal GMs, particularly poor repertoire GMs from preterm age to the fidgety period (12-15 weeks post-term age) (Bos *et al.,* 1998a; Garcia *et al.,* 2004; Zahed-Cheick *et al.,* 2011). Bos *et al.* (1998a) reported 79% abnormal GMs during preterm and 24% abnormal GMs at fidgety period (12-15 weeks post-term age). Garcia

et al. (2004) also reported a decreased proportion of abnormal GMs (60%) from preterm assessments to 46% at the fidgety period (12-15 weeks corrected age). Zahed-Cheick *et al.* (2011) reported a decreased proportion of abnormal GMs (73.6%) from preterm age to 21.2% at the fidgety period (12-15 weeks corrected age).

In the current study, of the six infants that scored absent fidgety movements (at 12-14 weeks post term age), five displayed poor-repertoire during their preterm to term age trajectories and one displayed cramped-synchronized GMs at the term age assessment. Thus, none of the infants with normal trajectories from preterm to term age had absent fidgety movements at 12-14 weeks post-term age. The absence of fidgety movements in all types of CP and different brain lesions, suggests that intact cortico-spinal fibers as well as output from the basal ganglia and cerebellum is needed to produce normal fidgety movements (Einspieler et al., 2002, 2004).

In the current study, one infant that displayed poor-repertoire on first assessment (birth to 33 weeks PMA), and subsequently scored cramped-synchronized at 34-37 weeks PMA, displayed normal fidgety movements at 12-14 weeks corrected age. As mentioned before, varying outcomes for transient cramped-synchronized GMs, including normal outcomes, CP and mild motor impairment have been reported (Cioni *et al.,* 1997b; Ferrari *et al.,* 2002; Mutlu *et al.,* 2010).

During the course of the current study, 12 infants passed away. Of these infants only one had a normal GM score during one of the preterm assessments. The other 11 infants all displayed abnormal GMs, including one with cramped-synchronized movements. The cause and time (PMA in weeks) of death in these infants was unknown.

5.3 Influence of perinatal risk factors on general movements (GMs)

Multivariable analysis of the association between certain perinatal risk factors and GM trajectories identified that birth weight and time (indicated as PMA in weeks) were inversely associated with an abnormal GM trajectory. This indicates that a lower birth weight and lower PMA were significantly associated with abnormal GMs (see Table 4.10). This outcome differs from other studies on the influence of perinatal factors on GMs (Zahed-Cheick *et al.,* 2011; Olsen *et al.,* 2015; Dostanic *et al.,* 2018). A recent study by Dostanic *et al*. (2018) included 144 twin infants and found that gestational age at birth correlated with abnormal GMs at term age and 12-14 weeks corrected age. Olsen *et al.*

(2015) found that infection was an independent variable associated with increased risk for abnormal GMs. The study by Zahed-Cheick *et al.* (2011) reported an association between abnormal preterm GMs and nosocomial infections. At the 12-14 weeks corrected age assessment, gestational age at birth correlated with an abnormal GM outcome. This finding could be attributed to the fact that Zahed-Cheick *et al.* (2011) only included EPT infants with a gestational age of 23-27 weeks, while the mean gestational age in the current study was 28.6 weeks.

The cohorts in the current and above-mentioned studies were quite similar in terms of birth weight. In the current study, the mean birth weight was 1048.2g while Olsen *et al.* (2015) reported a mean birth weight of 1024g and Zahed-Cheick *et al.* (2011) a slightly lower mean birth weight of 957g. Even with comparable mean birth weights, the study populations can still differ significantly. The birth weight in Dostanic *et al.* (2018) differs from the current study, due to the fact that they included twin pairs of preterm and term infants. The birth weight of the twin pairs ranged from 670g to 3820g (median 2323; IQR 645).

The reason for the difference in outcomes can be explained by the notable discrepancy in the time frame in which the GM trajectories were recorded. Dostanic *et al.* (2018) recorded GMs only from term age till 20 weeks post-term age, Olsen *et al.* (2015) recorded GMs from birth until term age only and Zahed-Cheick *et al.* (2011) only made video recordings at two time points, once during 30-40 weeks' gestation and once during the fidgety period (12-15 weeks corrected age).

The results from the current study are consistent with the findings of a recent study on risk factors associated with the quality of GMs (Ma *et al.,* 2018). Ma *et al.* (2018) assessed 618 infants at term age and 539 infants at 12-14 weeks corrected age and reported lower birth weight to be significantly associated with abnormal GMs at both time points. A review by Pascal *et al.* (2018) on the neurodevelopmental outcome of VLBW and VPT infants found that a decrease in birth weight is significantly associated with a higher prevalence of CP ($p<0.001$), as well as motor delays ($p=0.012$). A systematic review by Jarjour (2015) found that EPT infants with a higher birth weight had better rates of unimpaired survival.

To the best of our knowledge this is the largest study so far to report on GM trajectories measured at four key time points during preterm-, term- and 12-14 weeks corrected age.

This might explain why the current study is the first to report on time (PMA in weeks) as a significant variable associated with GM outcome (Table 4.10). De Vries *et al*. (2010) recorded serial GMs during the first 10 days of life in VPT and EPT infants. They found that abnormal GMs were significantly related to the earlier recording days. The younger the infants (PMA), the more often they presented with abnormal GMs. They concluded that an improvement in GM trajectories during the first week occurred in infants that had a higher birth weight and gestational age.

In the current study, gender was not a significant variable for the development of abnormal GMs. The cohort consisted of 53% female and 47% male infants (Table 4.1). Although gender was not associated with abnormal GMs, it should be noted that of the 12 infants that passed away during the course of the study, 75% (n=9) were male infants. Previous studies on trends of neonatal in-hospital morbidity (Elsmén, Hansen-Pupp & Hellstrom-Westas, 2004; Fanaroff, Stoll, Wright, Carlo, Ehrenkranz, Stark, Bauer, Donovan, Korones, Laptook, Lemons, Oh, Papile, Shankaran, Stevenson, Tyson & Poole, 2007; Kent *et al.,* 2011) have determined a significantly poorer outcome and survival rate for ELBW and preterm male infants. Furthermore, a recent systematic review has linked female gender to better long term neurodevelopmental outcomes (Jarjour, 2015).

Only one other study has reported on GMs in a HIV exposed cohort (Palchik, Einspieler, Evstafeyeva, Talisa & Marschik, 2013). Palchik *et al.* (2013) reported on a cohort that were HIV exposed and exposed to maternal opiates. They reported that HIV- and maternal opiate exposure were associated with an abnormal GM trajectory from term age till five months post-term age. At two to three year follow-up, 71% of infants exposed to maternal opiate abuse and HIV presented with a normal neurodevelopmental outcome (Plachik *et al.,* 2013). The current study is unique as 23% (n=27) of the cohort were HIV but not maternal opiate exposed. On univariable analysis, HIV was not significantly associated with an abormal GM trajectory (Table 4.9). A recent large prospective cohort study (n=670) found no clinically important differences in neurodevelopment at 24 months of age, assessed with the Bayley Scales of Infant and Toddler Development, Third Edition, between HIV exposed uninfected children compared to HIV unexposed uninfected children (Chaudhury, Williams, Mayondi, Leidner, Holding, Tepper, Nichols, Magetste, Sakoi, Moabi, Makhema, Mduli, Jubril, Seage, Kammere & Lockman, 2017).

Both IVH gr III and IV have been associated with neurological deficits and the development of CP, especially in ELBW infants (Volpe, 2009; Whitelaw 2011; Klebermass-Schrehof *et al.,* 2012). IVH gr III and IV have been associated with abnormal GM trajectories in preterm infants (Spittle *et al.,* 2008; Olsen *et al.,* 2015). On univariate analysis, IVH gr IV was a significant variable for an abnormal GM trajectory (Table 4.9). Only one infant had confirmed IVH gr IV (Table 4.3) and had abnormal GMs at term age and scored normal at 12-14 weeks post-term age. IVH gr III was not a significant variable for abnormal GM trajectory on univariate analysis (Table 4.9). Four infants had confirmed IVH gr III (Table 4.3) and all of them scored abnormal on GMAs during preterm assessments. Three of the four infants with IVH gr III scored normal at 12-14 weeks and one infant had absent fidgety movements. The small sample size of infants in the current study diagnosed with IVH gr III and IV may explain why IVH was not significantly associated with abnormal GM trajectories.

The evidence on infection as a significant factor associated with abnormal GMs is conflicting. Both Olsen *et al.* (2015) and Zahed-Cheick *et al.* (2011) found an association between post-natal infections and abnormal GMs. Bos *et al.* (1997b) reported that GM quality remained normal but had a “sluggish” character in infants with severe infections. In the current study, 37 infants were diagnosed with sepsis during their hospital stay (Table 4.3). However, on univariable analysis, sepsis was not significantly associated with abnormal GMs (Table 4.9).

5.4 Limitations of the study

The main limitation of the study was the decrease in the number of GMAs done from the first assessment (birth to 33 weeks PMA) (n=110) to the second assessment (34-37 weeks PMA) (n=47) and term age assessments (n=55). At TCH, once medically stable and reaching a weight of 1200g, infants were transferred to district hospitals and other lower care facilities. Infants were discharged home if medically stable and weighing more than 1800g. Follow up assessments had to be arranged in order to assess the infants at 34 weeks PMA to term age and at term age. In order to attend follow-up appointments, most of the parents/guardians of the infants made use of public transport, which in itself posed major challenges during the course of the study. During May, August and September the City of Cape Town was plagued by major bus strikes (Breytenbach, 2018:5), taxi strikes (Nienaber, 2018:1) as well as protest actions and riots which led to road closures of the major roads leading from the Cape Flats (Meyer & Marias, 2018:1).

During this time, taxi related violence also led to the weeklong closure of Bellville taxi rank, which is the main taxi rank servicing TCH (Palm, 2018). These taxi and bus strikes as well as riots threatened the safety of commuters and made it impossible for parents and their infants to attend follow up appointments. Parents that were not able to attend follow-up appointments, due to safety concerns, were asked to send a video recording of their infant via WhatsApp and were compensated for their data usage. However, not all parents had access to smartphones and WhatsApp, or the cell phone recordings were of such low quality that it was not possible to assess the video recording of GMs.

Australian researchers are currently conducting a research study on the potential of a smartphone app, the Baby Moves app, which provides a format for parents to upload videos of their infants' GMs. They hypothesized that since infants can be assessed remotely, it will be highly cost-effective in terms of reducing the need to attend clinics on-site for a GMA (Spittle, Olsen, Kwong, Doyle, Marschik, Einspieler & Cheong, 2016). This concept of using a smartphone app to conduct remote GMAs will only work in the South African context if parents have access to smartphones and internet data. The lack of outpatient follow-up may have reduced the number of normal GMs observed at 34-37 weeks PMA. This might explain why no normal GMs were observed at term age, since infants remaining in TCH had a more complicated medical history and therefore more likely to have abnormal GMs. Notwithstanding the setback of follow-up at preterm and term age, 88 infants were assessed at 12-14 weeks corrected age and a total of 300 assessments were conducted over the four key time periods.

It was not part of the scope of the current study to describe individual infant trajectories. Individual trajectories, especially for infants displaying temporary normal or cramped synchronized GMs prior to term or at term age, may provide a better understanding of the relationship between perinatal risk factors and GM quality.

Infants in the current study were only assessed until 12-14 weeks corrected age. Since it was not part of the scope of the current study, neurological assessments conducted at 12 and 24 months corrected age may be of value to describe the effect of GM trajectories and perinatal risk factors on long term neurodevelopmental outcomes.

CHAPTER 6

CONCLUSION AND RECOMMENDATIONS

The neonatal wards at TCH service an ever-increasing population and, due to limited resources, is under constant pressure to admit and care for VLBW and ELBW infants. Regardless of an improvement in perinatal care and survival rates, these infants remain at high-risk for long term developmental deficits (Larroque, Ancel, Marret, Marchand & Arnaud, 2008). It is thus of great importance for clinicians to identify those infants who will require early developmental follow up and intervention. This is the largest study so far assessing GMs at four key time periods from preterm till 12-14 weeks post-term age.

The results of this study found GMs predominantly abnormal during preterm and term age but mostly normal at 12-14 weeks corrected age. This result suggests that GMAs done prior to term age and at term age may not be clinically useful at TCH, as it is common for GMs to be abnormal at preterm and term age and the quality of GMs is likely to change over time. Preterm and term age GMAs are therefore less valuable for predicting neurodevelopmental outcomes in our study population.

Birth weight and time (PMA in weeks) were significantly associated with GM outcome. A lower birth weight is associated with higher odds for abnormal GMs trajectories. An increase in time (PMA in weeks) was associated with increased odds for normal GMs.

6.1 The clinical implications of preterm general movement assessments (GMAs)

The findings of this study have a number of important implications for future follow-up assessment of high-risk preterm infants at TCH. The results of the current study indicate that assessment of preterm and term GM trajectories does not necessarily enable earlier identification of infants at risk for neurodevelopmental difficulties. It is thus not clinically useful to allocate time and resources to conduct GM assessments prior to term age and at term age as GMs are likely to be abnormal or transition to normal over time. Prechtl's method of GMAs remains a quick, affordable and non-invasive assessment technique which makes it a good method to utilize at TCH. However, in high risk preterm infants GMAs should rather be implemented at 12-14 weeks corrected age as GMAs at preterm and term ages are likely to be abnormal and less discriminative for predicting

neurodevelopmental outcome. GMAs conducted at 12-14 weeks corrected age was previously proven to be of high predictive value at TCH (Burger *et al.,* 2007).

This study also suggests that infants with a lower birth weight should be targeted for more frequent follow up and neurological assessments as they remain the most at risk group for neurological deficits. This finding was also confirmed by Pascal *et al.,* (2018) reporting lower birth weight as a risk for later neurodevelopmental deficits.

6.2. Future research regarding the assessment of general movement (GM) trajectory

- It is important to establish the predictive value of GM trajectories, assessed at preterm, term and 12-14 weeks corrected age, on long term neurodevelopment. It will also be valuable to determine the significance of transient cramped-synchronized and normal GM trajectories for later neurodevelopment. Infants included in the current study are currently being followed up at 12 months corrected age to establish this relationship between GM trajectories and the fine motor, gross motor and cognitive development on the Griffiths Scales of Child Development, Third Edition.
- In order to establish the influence of perinatal factors on long term neurological outcome, individual infant trajectories should be described together with long term neurological follow up.
- Future research could include establishing the relationship between preterm and term age GMs and the motor optimality scores (MOS) at 12-14 weeks corrected age (http://general-movements-trust.info/5/home).
- The quality of GM trajectories, MOS and neurological outcome in HIV exposed but uninfected as well as HIV exposed and infected children is a largely under researched field.

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ADDENDUM A

HEALTH RESEARCH ETHICS COMMITTEE APPROVAL LETTER

UNIVERSITEIT
STELLENBOSCH
UNIVERSITY

Approved

New Application

Health Research Ethics Committee (HREC)

27/10/2017

Project Reference #: 0988

HREC Reference #: S17/08/142

Title: The trajectory of general movements from birth until 12-14 weeks corrected age in preterm infants born before 33 weeks' gestation and weighing less than 1500g: a descriptive study

Dear Miss Reze van Zyl

The **New Application** received on 02/10/2017 08:41 was reviewed by the **Health Research Ethics** via **expedited** review procedures on 27 October 2017 and was approved.

Please note the following information about your approved research protocol:

Protocol Approval Period: **This project has approval for 12 months from the date of this letter.**

Please remember to use your HREC reference **number** (S17/08/142 S17/08/142) on any documents or correspondence with the HREC concerning your research protocol.

Please note that this decision will be ratified at the next HREC full committee meeting. HREC reserves the right to suspend the approval and to request changes or clarifications from applicants. The coordinator will notify the applicant (and if applicable, the supervisor) of the changes or suspension within 1 day of receiving the notice of suspension from HREC. HREC has the prerogative and authority to ask further questions, seek additional information, require further modifications, or monitor the conduct of your research and the consent process.

After Ethical Review

Please note you can submit your progress report through the online ethics application process, available at: https://apply.ethics.sun.ac.za and the application should be submitted to the Committee before the year has expired. Please see Forms and Instructions on our HREC website for guidance on how to submit a progress report.

The Committee will then consider the continuation of the project for a further year (if necessary). Annually a number of projects may be selected randomly for an external audit.

Translation of the consent document(s) to the language(s) applicable to your study participants should now be submitted to the HREC.

Provincial and City of Cape Town Approval

Please note that for research at a primary or secondary healthcare facility, permission must still be obtained from the relevant authorities (Western Cape Department of Health and/or City Health) to conduct the research as stated in the protocol. Please consult the Western Cape Government website for access to the online Health Research Approval Process, see: https://www.westerncape.gov.za/general-publication/health-research-approval-process. Research that will be conducted at any tertiary academic institution requires approval from the relevant hospital manager. Ethics approval is required BEFORE approval can be obtained from these health authorities.

We wish you the best as you conduct your research.

For standard HREC forms and instructions, please visit: Forms and Instructions on our HREC website (www.sun.ac.za/healthresearchethics)

ADDENDUM B

Western Cape Department of Health Approval Letters:

Tygerberg-, Eersterivier-, Karl Bremer- and Khayelitsha Hospitals

Western Cape Government
Health

TYGERBERG HOSPITAL
REFERENCE:
Research Projects
ENQUIRIES: [redacted]
[redacted]
TELEPHONE [redacted]

Ethics Reference: **S17/08/142**

TITLE: The trajectory of general movements from birth until 12-14 weeks corrected age in preterm infants born before 33 weeks' gestation and weighing less than 1500g: a descriptive study.

Dear Miss Reze van Zyl

PERMISSION TO CONDUCT YOUR RESEARCH AT TYGERBERG HOSPITAL.

1. In accordance with the Provincial Research Policy and Tygerberg Hospital Notice No 40/2009, permission is hereby granted for you to conduct the above-mentioned research here at Tygerberg Hospital.

2. Researchers, in accessing Provincial health facilities, are expressing consent to provide the Department with an electronic copy of the final feedback within six months of completion of research. This can be submitted to the Provincial Research Co-Ordinator (Health.Research@westerncape.gov.za).

[redacted]

MANAGER: MEDICAL SERVICES

[redacted]

CHIEF EXECUTIVE OFFICER
Date: 5 December 2017

Administration Building, Francie van Zijl Avenue, Parow, 7500 Private Bag X3, Tygerberg, 7505
tel: +27 21 938-6267 fax: +27 21 938-4890 www.capegateway.go.v.za

TYGERBERG HOSPITAL

Ethics Reference: **S17/08/142**

TITLE: The trajectory of general movements from birth until 12-14 weeks corrected age in preterm infants born before 33 weeks' gestation and weighing less than 1500g: a descriptive study.

BY [redacted]
An authorized representative of Tygerberg Hospital

NAME [redacted]

TITLE [redacted]

DATE 6 December 2017

Health impact assessment
Health research sub directorate
Health.Research@westerncape.gov.za
Tel: +27 21 483 0866: fax: +27 21 483 9895
5th Floor, Norton Rose House, 8 Riebeek Street, Cape Town, 8001
www.capegateway.gov.za)

REFERENCE: WC_201711_004
ENQUIRIES: [redacted]

Stellenbosch University

Francie Van Zijl Drive

Tygerberg Hospital

Cape Town

7505

For attention: Ms Reze van Zyl, [redacted]

Re: The Trajectory Of General Movements From Birth Until 12-14 Weeks Corrected Age In Preterm Infants Born Before 33 Weeks' Gestation And Weighing Less Than 1500g: A Descriptive Study.

Thank you for submitting your proposal to undertake the above-mentioned study. We are pleased to inform you that the department has granted you approval for your research. Please contact following people to assist you with any further enquiries in accessing the following sites:

[redacted] [redacted] [redacted]

Kindly ensure that the following are adhered to:

1. Arrangements can be made with managers, providing that normal activities at requested facilities are not interrupted.
2. Researchers, in accessing provincial health facilities, are expressing consent to provide the department with an electronic copy of the final feedback (**annexure 9**) within six months of completion of research. This can be submitted to the provincial Research Co-ordinator (Health.Research@westerncape.gov.za).

3. In the event where the research project goes beyond the *estimated completion* date which was submitted, researchers are expected to complete and submit a progress report (**Annexure 8**) to the provincial Research Co-ordinator (Health.Research@westerncape.gov.za).

4. The reference number above should be quoted in all future correspondence.

Yours sincerely

DIRECTOR: HEALTH IMPACT ASSESSMENT

DATE: 9/2/2018.

Western Cape Government
Health

Health impact assessment
Health research sub directorate
Health.Research@westerncape.gov.za
Tel: +27 21 483 0866; fax: +27 21 483 9895
5th Floor, Norton Rose House, 8 Riebeek Street, Cape Town, 8001
www.capegateway.gov.za)

REFERENCE: WC_201711_004
ENQUIRIES: [redacted]

Stellenbosch University

Francie Van Zijl Drive

Tygerberg Hospital

Cape Town

7505

For attention: Ms Reze van Zyl, [redacted]

Re: The Trajectory Of General Movements From Birth Until 12-14 Weeks Corrected Age In Preterm Infants Born Before 33 Weeks' Gestation And Weighing Less Than 1500g: A Descriptive Study.

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[redacted] [redacted] [redacted]

Kindly ensure that the following are adhered to:

1. Arrangements can be made with managers, providing that normal activities at requested facilities are not interrupted.
2. Researchers, in accessing provincial health facilities, are expressing consent to provide the department with an electronic copy of the final feedback (**annexure 9**) within six months of completion of research. This can be submitted to the provincial Research Co-ordinator (Health.Research@westerncape.gov.za).

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4. The reference number above should be quoted in all future correspondence.

Yours sincerely

[redacted]

DIRECTOR: HEALTH IMPACT ASSESSMENT

DATE: 9/2/2018

Western Cape Government
Health

Health impact assessment
Health research sub directorate
Health.Research@westerncape.gov.za
Tel: +27 21 483 0866; fax: +27 21 483 9895
5th Floor, Norton Rose House, 8 Riebeek Street, Cape Town, 8001
www.capegateway.gov.za)

REFERENCE: WC_201711_004
ENQUIRIES: [redacted]

Stellenbosch University

Francie Van Zijl Drive

Tygerberg Hospital

Cape Town

7505

For attention: Ms Reze van Zyl, [redacted]

Re: The Trajectory Of General Movements From Birth Until 12-14 Weeks Corrected Age In Preterm Infants Born Before 33 Weeks' Gestation And Weighing Less Than 1500g: A Descriptive Study.

Thank you for submitting your proposal to undertake the above-mentioned study. We are pleased to inform you that the department has granted you approval for your research. Please contact following people to assist you with any further enquiries in accessing the following sites:

[redacted]

Kindly ensure that the following are adhered to:

1. Arrangements can be made with managers, providing that normal activities at requested facilities are not interrupted.
2. Researchers, in accessing provincial health facilities, are expressing consent to provide the department with an electronic copy of the final feedback (**annexure 9**) within six months of completion of research. This can be submitted to the provincial Research Co-ordinator (Health.Research@westerncape.gov.za).

3. In the event where the research project goes beyond the *estimated completion* date which was submitted, researchers are expected to complete and submit a progress report (**Annexure 8**) to the provincial Research Co-ordinator (Health.Research@westerncape.gov.za).

4. The reference number above should be quoted in all future correspondence.

Yours sincerely

[redacted]

DIRECTOR: HEALTH IMPACT ASSESSMENT

DATE: 6/3/2018.

ADDENDUM C

PARTICIPATION INFORMATION LEAFLET AND CONSENT FORM

English and Afrikaans

PARTICIPANT INFORMATION LEAFLET AND CONSENT FORM

TITLE OF THE RESEARCH PROJECT:

The trajectory of general movements from birth until 12-14 weeks corrected age in preterm infants born before 33 weeks' gestation and weighing less than 1500g: a descriptive study.

REFERENCE NUMBER:

PRINCIPAL INVESTIGATOR: Reze van Zyl

ADDRESS: Physiotherapy Division
Medical School; Stellenbosch University
Francie Van Zijl Drive
Tygerberg
7505
Cape Town
South Africa

CONTACT NUMBER:

You are being invited to take part in a research project. Please take some time to read the information presented here, which will explain the details of this project. Please ask the study investigator any questions about any part of this project that you do not fully understand. It is very important that you are fully satisfied that you clearly understand what this research entails and how you could be involved. Also, your participation is **entirely voluntary** and you are free to decline to participate. If you say no, this will not affect you negatively in any way whatsoever. You are also free to withdraw from the study at any point, even if you do agree to take part.

This study has been approved by the **Health Research Ethics Committee at Stellenbosch University** and will be conducted according to the ethical guidelines and principles of the international Declaration of Helsinki, South African Guidelines for Good Clinical Practice and the Medical Research Council (MRC) Ethical Guidelines for Research.

What is this research study all about?

- The study will take place at Tygerberg Children's Hospital (TCH), Bellville, Cape Town.
- The aim of the project is to determine the progression of spontaneous movements displayed by my preterm born infant. These movement patterns are linked to further functional development of the infant. For us to understand this link even better, we are investigating these spontaneous movements in more detail.
- The researcher will take video recordings of 5 to 15 minutes of your child at three to four different age time points, namely a week after birth, just before discharge to Karl Bremer, Eerste Rivier or Khayelitsha Hospitals or at these hospitals. The

final video recording will be made at the Neonatal High Risk Clinic (Paediatric Outpatients, C3A) of TCH during your baby's three months corrected visit.

- During the recording my child will be fully, but lightly dressed. I may be present during the video recording, but will be asked not to interact with my baby during the assessment. The video recording will be made available for me to view immediately after the initial assessment.
- Each video recording obtained during the course of the study will be kept safely and secured. During the study, all gathered information will be coded so that the information regarding your child will only be known to the researcher. After the final assessment, the video recordings of your child will be destroyed.

Why have you been invited to participate?

- Your child fit the criteria of infants we would like to assess in the study, namely :
  - Your child was born preterm (before 33 weeks' gestation) and admitted to TCH.
  - Your child weighed less than 1500g at birth.
  - You stay in one of the area's close to TCH.

What will your responsibilities be?

- Your responsibility will only be to make your child available for the video recordings and console the child when needed.

Will you benefit from taking part in this research?

- If any abnormality is noted in the spontaneous movements of your child, the researcher will inform you and refer you to appropriate health care practitioners.
- Future preterm babies may benefit from the study as this will lead to a better understanding of their early development and earlier identification of babies that may require therapeutic intervention.

Are there in risks involved in your taking part in this research?

- Your child's participation in the study does not present any risks to him/her.

If you do not agree to take part, what alternatives do you have?

- If you do not wish for your child to take part in this study or feel the need to withdraw him/her at any stage, there will be no negative consequences to him/her. Participation is completely voluntary.

Who will have access to your medical records?

- The information collected will be coded and treated as confidential. Information will be protected at all times. If it is used in a publication or thesis, the identity of your child will remain anonymous. Only the researcher, assessors and the healthcare staff who already have access to your child's medical records, will have access to the medical records.

What will happen in the unlikely event of some form injury occurring as a direct result of your taking part in this research study?

- In the unlikely event of an injury, participants will be treated by the nursing staff or Doctors at TCH.

Will you be paid to take part in this study and are there any costs involved?

- No, you will not be paid to take part in the study while your baby is still hospitalized in TCH, Karl Bremer Hospital, Eerste Rivier Hospital or Khayelitsha Hospital. You will however, receive remuneration in the form of a R100.00 voucher at a local, accessible grocery store upon follow up visits to the Neonatal High Risk Clinic, Paediatric Outpatients C3A, TCH (after discharge from Karl Bremer, Eerste Rivier and Khayelitsha Hospitals). There will be no costs involved for you, if you do take part.

Is there anything else that you should know or do?

- You can contact the Health Research Ethics Committee at 021-938 9207 if you have any concerns or complaints that have not been adequately addressed by your study investigator. .
- You will receive a copy of this information and consent form for your own records.

Declaration by participant

By signing below, I ……..……. agree to take part in a research study entitled *(insert title of study)*.

I declare that:

- I have read or had read to me this information and consent form and it is written in a language with which I am fluent and comfortable.
- I have had a chance to ask questions and all my questions have been adequately answered.
- I understand that taking part in this study is **voluntary** and I have not been pressurised to take part.
- I may choose to leave the study at any time and will not be penalised or prejudiced in any way.
- I may be asked to leave the study before it has finished, if the study doctor or researcher feels it is in my best interests, or if I do not follow the study plan, as agreed to.

Signed at (*place*) .....…..…….. on (*date*) ……...…….. 2017.

....

Signature of participant **Signature of witness**

Declaration by investigator

I *(name)* ……..…… declare that:

- I explained the information in this document to ……..
- I encouraged him/her to ask questions and took adequate time to answer them.
- I am satisfied that he/she adequately understands all aspects of the research, as discussed above
- I did/did not use a interpreter. (*If a interpreter is used then the interpreter must sign the declaration below.*

Signed at (*place*) .....…….....…….. on (*date*) ……...…….. 2017.

....
Signature of investigator **Signature of witness**

Declaration by interpreter

I *(name)* ……..…… declare that:

- I assisted the investigator (*name*) ……. to explain the information in this document to (*name of participant*) ……..…….. using the language medium of Afrikaans/Xhosa.
- We encouraged him/her to ask questions and took adequate time to answer them.
- I conveyed a factually correct version of what was related to me.
- I am satisfied that the participant fully understands the content of this informed consent document and has had all his/her question satisfactorily answered.

Signed at (*place*) .....…….....…….. on (*date*) ……...……..

....
Signature of interpreter **Signature of witness**

DEELNEMERINLIGTINGSBLAD EN TOESTEMMINGSVORM

TITEL VAN DIE NAVORSINGSPROJEK:

Die verloop van algemene bewegings vanaf geboorte tot en met 12-14 weke gekorrigeerde ouderdom in preterm baba's gebore voor 33 weke gestasie en wat minder as 1500 gram weeg: 'n beskrywende studie.

VERWYSINGSNOMMER: 0988

HOOFNAVORSER: Reze van Zyl

ADRES: Fisioterapie Afdeling
Mediese kampus; Universiteit van Stellenbosch
Francie Van Zijl Rylaan
Tygerberg
7505
Cape Town
South Africa

KONTAKNOMMER:

U word genooi om deel te neem aan 'n navorsingsprojek. Lees asseblief hierdie inligtingsblad op u tyd deur aangesien die detail van die navorsingsprojek daarin verduidelik word. Indien daar enige deel van die navorsingsprojek is wat u nie ten volle verstaan nie, is u welkom om die navorsingspersoneel of dokter daaroor uit te vra. Dit is baie belangrik dat u ten volle moet verstaan wat die navorsingsprojek behels en hoe u daarby betrokke kan wees. U deelname is ook **volkome vrywillig** en dit staan u vry om deelname te weier. U sal op geen wyse negatief beïnvloed word indien u sou weier om deel te neem nie. U mag ook te eniger tyd aan die navorsingsprojek onttrek, selfs al het u ingestem om deel te neem.

Hierdie navorsingsprojek is deur die **Gesondheids Navorsings Etiek Komitee (GNEK) van die Universiteit Stellenbosch** goedgekeur en sal uitgevoer word volgens die etiese riglyne en beginsels van die Internasionale Verklaring van Helsinki en die Riglyne vir Navorsing van die Mediese Navorsingsraad (MNR).

Wat behels hierdie navorsingsprojek?

- Die navorsingsprojek sal uitgevoer word by Tygerberg Kinderhospitaal, Bellville, Kaapstad.
- Die doelwit van die projek is om die progressie van die spontane bewegingspatrone (van die ledemate en romp) van die baba wat preterm gebore is waar te neem. Hierdie bewegingspatrone hou verband met verdere ontwikkeling van die baba. Vir ons om hierdie verwantskap beter te verstaan wil ons hierdie spontane bewegings in meer detail ondersoek.
- Die navorser gaan video opnames neem van 5 tot 10 minute van u baba, tydens drie tot vier verskillende ouderdomstydperke, naamlik een week na geboorte, net

voor ontslag na Karl Bremer, Eerste Rivier of Khayelitsha Hospitale of by die hospitale. Die finale video opname sal plaasvind tydens u baba se drie maande (gekorrigeerde ouderdom) besoek by die Neonatale Hoë Risiko Kliniek (Pediatrie buite-pasiënte, C3A) van Tygerberg Kinderhospitaal.

- Tydens die opname sal my baba ten volle, maar ligweg aangetrek wees. Ek mag teenwoordig wees tydens die maak van die opname, maar sal gevra word om nie met die baba interaksie te hê tydens die opname nie. Die opname sal aan my gewys word direk na die oorspronklike evaluering.
- Elke video wat tydens die verloop van die projek gemaak word, sal veilig bewaar word. Alle inligting wat gedurende die projek versamel word, sal met behulp van 'n kode-sisteem hanteer word sodat alle informasie in verband met u kind slegs aan die navorser bekend sal wees. Nadat die navorsings projek afgehandel is, sal die videos van kant gemaak word.

Waarom is u genooi om deel te neem?

- U kind voldoen aan die kriteria van babas wat ons wil evalueer in die projek, naamlik:
  - U kind was preterm gebore (voor 33 weke gestasie) en toegelaat in Tygerberg Kinderhospitaal.
  - U kind het met geboorte minder as 1500 gram geweeg.
  - U is woonagtig in 'n area naby aan Tygerberg Kinderhospitaal (die Noordelike Voorstede van Kaapstad of die Kaapse Vlakte).

- Indien u kind in 2017 gebore was en tans drie maande of ouer is, kan u kind steeds deelneem in die projek:
  - Ons sal gebruik maak van die video opnames wat reeds van u baba gemaak is voor en tydens volterm en met u drie maande opvolg besoek. Hierdie video opnames vorm deel van die standaard neonatale evaluerings protokol van Tygerberg Kinderhospitaal en sal gebruik word om u baba se bewegingspatrone te evalueer.

.

Wat sal u verantwoordelikhede wees?

- U verantwoordelikheid sal slegs wees om u baba vir die opnames beskikbaar te stel en te troos indien dit benodig word.

Sal u voordeel trek deur deel te neem aan hierdie navorsingsprojek?

- Indien enige abnormaliteit in die bewegingspatrone van u kind opgemerk word, sal die navorser u inlig en na die toepaslike gesondheidsorg personeel verwys.
- Toekomstige prematuur gebore babas mag baat vind by die projek aangesien dit sal lei tot 'n beter insig van hul vroeë ontwikkeling en vroeër identifisering van babas wat terapie sal benodig.

.

Is daar enige risiko's verbonde aan u deelname aan hierdie navorsingsprojek?

- Die deelname van u baba aan die projek voorspel geen risiko's aan hom/haar.

Watter alternatiewe is daar indien u nie instem om deel te neem nie?

- Indien u verkies dat u baba nie deelneem aan die projek nie of u voel tydens die verloop van die projek om hom/haar te onttrek, sal dit geen negatiewe gevolge vir hom/haar inhou nie. Deelname is ten volle vrywillig.

Wie sal toegang hê tot u mediese rekords?

- Alle inligting wat versamel word sal gekodeer word en as konfidensieel hanteer word. Die inligting sal ten alle tye bewaar word. Indien dit gebruik word tydens publikasie of tesis sal die identiteit van u baba anoniem gehou word. Slegs die navorser, assessors en gesondheidspersoneel wat alreeds toegang het tot u baba se mediese inligting sal toegang hê tot die mediese verslae.

Wat sal gebeur in die onwaarskynlike geval van 'n besering wat mag voorkom as gevolg van u deelname aan hierdie navorsingsprojek?

- In die onwaarskynlike geval van 'n besering sal u kind versorg word deur die verpleegsters en dokters by Tygerberg Kinderhospitaal.

Sal u betaal word vir deelname aan die navorsingsprojek en is daar enige koste verbonde aan deelname?

- Nee, u gaan geen betaling ontvang vir deelname aan die projek nie. Daar gaan geen kostes vir u wees indien u deelneem aan die projek nie.

Is daar enigiets anders wat u moet weet of doen

- U kan die Gesondheids Navorsings Etiek Komitee (GNEK) kontak by 021-938 9207 in die u enige bekommernisse of klagtes het wat nie voldoene aangespreek was deur die navorser nie.
- U sal 'n kopie van hierdie inligtingsblad en toestemmingsvorm ontvang.

Verklaring deur deelnemer

Met die ondertekening van hierdie dokument onderneem ek,....., om my baba te laat deel te neem aan 'n navorsingsprojek getiteld: *Die verloop van algemene bewegings vanaf geboorte tot en met 12-14 weke gekorrigeerde ouderdom in preterm baba's gebore voor 33 weke gestasie en wat minder as 1500 gram weeg: 'n beskrywende studie.*

Ek verklaar dat:

- Ek hierdie inligtings- en toestemmingsvorm gelees het of aan my laat voorlees het en dat dit in 'n taal geskryf is waarin ek vaardig en gemaklik mee is.
- Ek geleentheid gehad het om vrae te stel en dat al my vrae bevredigend beantwoord is.
- Ek verstaan dat deelname aan hierdie navorsingsprojek **vrywillig** is en dat daar geen druk op my geplaas is om deel te neem nie.
- Ek te eniger tyd aan die navorsingsprojek mag onttrek en dat ek nie op enige wyse daardeur benadeel sal word nie.

- Ek gevra mag word om van die navorsingsprojek te onttrek voordat dit afgehandel is indien die studiedokter of navorser van oordeel is dat dit in my beste belang is, of indien ek nie die ooreengekome navorsingsplan volg nie.

Geteken te (*plek*) .....…..…….. op (*datum*) ……..…….. 2018.

....
Handtekening van deelneemer **Handtekening van getuie**

Verklaring deur navorser

Ek *(naam)* ……..…… verklaar dat:

- Ek die inligting in hierdie dokument verduidelik het aan .....
- Ek hom/haar aangemoedig het om vrae te vra en voldoende tyd gebruik het om dit te beantwoord.
- Ek tevrede is dat hy/sy al die aspekte van die navorsingsprojek soos hierbo bespreek, voldoende verstaan.
- Ek 'n tolk gebruik het/nie 'n tolk gebruik het nie. *(Indien 'n tolk gebruik is, moet die tolk die onderstaande verklaring teken.)*

Geteken te (*plek*) .....…..…….. op (*datum*) ……..…….. 2018.

....
Verklaring deur navorser **Verklaring deur getuie**

Verklaring deur tolk

Ek *(naam)* ……..…… verklaar dat:

- Ek die navorser *(naam)*..... bygestaan het om die inligting in hierdie dokument in Afrikaans/Xhosa aan *(naam van deelnemer)*..... te verduidelik.
- Ons hom/haar aangemoedig het om vrae te vra en voldoende tyd gebruik het om dit te beantwoord.
- Ek 'n feitlik korrekte weergawe oorgedra het van wat aan my vertel is.
- Ek tevrede is dat die deelnemer die inhoud van hierdie dokument ten volle verstaan en dat al sy/haar vrae bevredigend beantwoord is.

Geteken te (*plek*) .....…….. op (*datum*) ……..……..2018.

....

Handtekenig van tolk **Handtekening van getuie**