Neurodevelopmental Outcome of the High Risk Infant in Cape Town

Mary Clare Thompson

MB ChB (Cape Town), DCH (SA)

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Declaration

I, Mary Clare Thompson, hereby declare that this thesis is my own work and has not been presented for any degree at another university. The work for this thesis was performed in the Department of Paediatrics, University of Cape Town.

Signed: Signed by candidate
Signature removed

Date: 1/7/2001

To Roy, Nicholas and Timothy

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Abstract

The outcome of high risk infants provides an important audit of neonatal care. This audit renders valuable information to clinicians, parents and health care planners. Available outcome data from the developing world are sparse and urgently needed. This work was compiled with three aims in mind: to provide data from Cape Town on outcome of high risk infants (including both infants of very low birthweight and infants who have survived hypoxic ischaemic encephalopathy); to evaluate selected early neurodevelopmental assessments of these infants; and to propose a protocol for their effective follow-up. Three separate cohorts were selected and studied in order to achieve these aims.

A prospective six year follow-up study of infants with birth weights less than 1250 g was undertaken at Groote Schuur Hospital's Neonatal Intensive Care Unit. The aim of the study was to document the morbidity, mortality and neurodevelopmental outcome of these infants.

Of 235 liveborn infants, 143 (61%) survived to discharge. Better survival was documented for infants who weighed more than 900 g and were over 30 weeks gestation and whose mothers attended antenatal care.

One hundred and six infants (83% of survivors) underwent clinical assessment at one year of age and were evaluated with the Griffiths Scales of Mental Development. Ninety six (91%) of these survivors were seen and tested at two years of age and 80 (76%) were seen at six years of age together with 70 matched controls who had normal birthweights.

Of the 106 infants assessed at one year of age, six infants were diagnosed as cerebral palsied, six were globally developmentally delayed without signs of cerebral palsy and one infant showed significant motor delay with a normal developmental quotient. At two years of age one further infant had cerebral palsy and nine more infants were developmentally delayed. At six years of age five infants had cerebral palsy, one was intellectually disabled and three were intellectually borderline. The major disability rate at one year of age was 11%, at two years of age was 22%

and at six years of age was eight percent. The incidence of low birthweight children with possible learning disability was three times that of their matched controls and overall, the low birthweight children scored significantly less in all developmental measures.

Forty-five infants who developed hypoxic ischaemic encephalopathy after birth were studied prospectively. A numeric scoring system for the assessment of hypoxic ischaemic encephalopathy during the neonatal period which had previously been developed at Groote Schuur Hospital was tested. The value of the score in predicting neurodevelopmental outcome at one year of age was assessed. Thirty five infants were evaluated at 12 months of age by full neurological examination and the Griffiths Scales of Mental Development. Five infants were assessed at an earlier stage, 4 who died before 6 months of age and one infant who was hospitalised at the time of the 12 month assessment. Twenty three (58%) of the infants were normal, 17 (42%) were abnormal, 16 with cerebral palsy and one with developmental delay. 25 infants were re-evaluated at 3 years of age. 15 of these 25 had been normal at one year of age and were evaluated with ten controls who had had an uneventful perinatal course.

The Hypoxic Ischaemic Encephalopathy Score was highly predictive for outcome. The best correlation with outcome was a combination of the peak score and evaluation on day seven; giving a positive predictive value of 92% and a negative predictive value of 100% for abnormal outcome, with a sensitivity of 100% and specificity of 93%. At three years of age the HIE survivors without cerebral palsy scored as well as their matched controls on Griffiths developmental evaluation. In these normal survivors no correlation between severity of HIE and developmental quotient was demonstrated.

Infants with neurodevelopmental abnormality need to start therapy early and because of this, should be detected as soon as possible. Currently, no widely accepted method of early evaluation exists. A Perinatal Risk Rating, the Dubowitz Neurological Assessment and the Infant Neuromotor Assessment were compared in terms of predicting neurodevelopmental outcome at one year of age.

A cohort of 130 consecutive neonatal intensive care unit graduates were selected according to high risk criteria. Each infant was examined at term gestational age on the Dubowitz Neurological Assessment and a Perinatal Risk Rating was allocated. The study infants were seen again at 18 weeks corrected age, when an Infant Neuromotor Assessment was done, and at one year of age the Griffiths Scales of Mental Developmental and full neurological examination were carried out.

Of the 130 infants assessed at term, all were seen at 18 weeks. Thereafter five were lost to follow-up and two died. The outcome of all the remaining 123 infants is known.

Prediction of a normal outcome at 1 year of age on the Dubowitz Neurological Assessment was 96% and for the Perinatal Risk Rating, 98%, but for an abnormal outcome they predicted only 56% and 42% respectively. The Infant Neurological Assessment at 18 weeks of age predicted a normal outcome at one year in 99% and an abnormal outcome in 82%.

Very low birthweight infants are at higher risk for cerebral palsy and intellectual disability. In Groote Schuur Hospital, at six years of age, the major disability rate for infants with birthweights less than 1250 g was eight percent. Forty percent of term infants who survived hypoxic ischaemic encephalopathy had cerebral palsy with associated intellectual disability. The use of the Perinatal Risk Rating is appropriate in newborn facilities where cranial ultrasound is available. Otherwise the Dubowitz Neurological Assessment is an appropriate screening tool in the newborn period. Use of the Hypoxic Ischaemic Encephalopathy Score is recommended for clinical evaluation, prognostication and risk rating.

It is proposed that high risk infants should be evaluated at 18 weeks corrected age with the Infant Neuromotor Assessment at a tertiary centre. If this assessment is normal, the infant can then be discharged to community clinic follow-up. Infants with more than one deviant sign at this age need continued review and those with more than three signs should be referred for neurodevelopmental therapy to a comprehensive neurodevelopmental clinic. Even those high risk infants whose assessments are normal should be enrolled in a pre-school centre at five years of age to facilitate detection of learning problems prior to school entry.

Contents

List of abbreviations

ADH	Attention deficit and hyperactivity
BD	Base deficit
BPD	Broncho-pulmonary dysplasia
BW	Birthweight
CRIB	Clinical risk index for babies
CP	Cerebral palsy
CT	Computerised tomography
C/S	Caesarean section
DQ	Developmental quotient
DNA	Dubowitz Neurological Assessment
aEEG	Amplitude integrated electroencephalogram
EEG	Electroencephalogram
ELBW	Extremely low birthweight
E/H	Eye hand quotient
FAS	Fetal alcohol syndrome
FiO2	Inspired oxygen concentration
Font'l	Fontanelle tension
g	Grams
GA	Gestational age
GIQ	General intelligence quotient
GSH	Groote Schuur Hospital
GPH	Gestational proteinuric hypertension
GQ	General quotient
H/S	Hearing and speech quotient
HIE	Hypoxic ischaemic encephalopathy
HMD	Hyaline membrane disease
ID	Intellectual disability
IMR	Infant mortality rate
INA	Infant Neuromotor Assessment
IPPV	Intermittent positive pressure ventilation
IQ	Intelligence quotient
IVH	Intra-ventricular haemorrhage
JSAIS	Junior South African Intelligence Scales
LBW	Low birthweight
LBWR	Low birthweight rate
LDC's	Least developed countries
LOC	Locomotor quotient
Loc	Level of consciousness
MOU	Midwife Obstetric Unit

MMR	Maternal mortality rate
MRu5	Mortality rate under five years of age
n	Number
ND	Neurodevelopment
NDT	Neurodevelopmental therapy
NEC	Necrotising enterocolitis
NICU	Neonatal intensive care unit
NPV	Negative predictive value
NS	Not significant
NVD	Normal vaginal delivery
PaCO2	Arterial carbon dioxide concentration
Perf	Performance quotient
PMNS	Peninsula Maternal and Neonatal Service
PNMR	Perinatal mortality rate
PPV	Positive predictive value
P/S	Personal/social quotient
PR	Practical reasoning quotient
PRR	Perinatal Risk Rating
PV-IVH	Periventricular - intraventricular haemorrhage
PVL	Peri-ventricular leucomalacia
Resp	Respiratory pattern
ROP	Retinopathy of prematurity
SCL	Subcortical leucomalacia
SD	Standard deviation
SIDS	Sudden Infant Death Syndrome
SR	Survival rate
S & H	Speech and hearing
UGA	Underweight for gestational age
VLBW	Very low birthweight

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Chapter 1

Introduction

While a progressive increase in knowledge and treatment techniques in neonatology has led to the improved survival of newborn infants in recent years, how much is neonatal intensive care adding to the burden of disabled children? Do most intensive care survivors grow up as healthy children with a capacity for learning and the ability to become productive, independent adults? These questions have led to the need for neurodevelopmental follow-up of intensive care survivors and contributed to the expanding field of developmental paediatrics.

Neonatal intensive care endeavours to ensure the survival of infants who develop life threatening complications following birth. Initially, the concerns of the parents and medical staff are centred on infant survival. Later, when the crisis has passed, the focus of concern shifts to the possibility of survival with developmental complications. When the outcome is unfavourable, the task does not end with the discharge of the infant from the Intensive Care Unit, but by necessity it involves support for the parents in their grief at the loss of normality in their child. Their grief is accompanied by a life-long burden of caring for their child. Early assessment of neurodevelopmental outcome is valuable for both the child and the family so that therapies can be instituted as soon as possible and later complications of secondary disabilities can be avoided.

Evaluating the outcome of high risk infants provides an important audit of neonatal care in a particular hospital or geographical area. It also enables clinicians to predict what proportion of the infants will require ongoing care after hospital discharge. It gives parents an indication of what to expect with their high risk infants and allows them to prepare for an unfavourable outcome if it appears likely. More importantly, this kind of audit is necessary for planning health care needs.

World literature abounds with information on outcome of high risk infants (Escobar et al, 1991; Aylward et al, 1989; Ornstein et al, 1991). Most published studies have been carried out in

sophisticated units where special investigations and highly technical management modalities are the norm (Victorian Infant Collaborative Study Group, 1991; Marlow et al, 1987; Kitchen et al, 1991). Data on outcome of these infants in Southern Africa are sparse (Molteno et al, 1980; Cooper et al, 1997, Kirsten et al 1995)). Here the incidence of birth asphyxia in the term infant, often with disabling neurological consequences, is higher than in developed countries (Molteno and Lachman, 1996; Airede and Weerasinghe, 1995). Frequently, the impact of a damaged child on the family is aggravated by the stresses of poverty. It is also compounded by the lack of health services. In order to begin planning facilities for disabled children, it is imperative that the number of children requiring such services is known or can be anticipated. Initially, scarce resources for these infants need to be reserved for those most in need. For these reasons there is an urgent need to compile neurodevelopmental outcome data in the Southern African region.

The setting

The continent of Africa, with a population of 771 million, comprises a number of developing countries. South Africa has a population of 42.6 million and is one of the more populous (Population Reference Bureau, 1999). The population density of South Africa is 90 persons per square mile (m^2), compared to 96 / m^2 in East Africa and 94 / m^2 in West Africa. The country with the highest population density is Rwanda (802 / m^2).

Recent data from the World Health Organisation (The World Health Report, 1998) collates health indicators for the world's population. Countries are grouped according to their economic status into two groups and subdivided thereafter as shown in table 1.I

Common indicators used to measure a country's health are Infant Mortality Rate (IMR) and the Mortality Rate under 5 years of age (MRu5). Table 1.II shows the WHO 1998 figures (these are estimates) for IMR and MRu5 for selected countries. All indicators are quoted per thousand live births. A comparison can be made between African countries and their developed counterparts.

Table 1.I : World economic grouping, World Health Report 1998

Developed World		Developing world	
Developed Market Economies	**Economies in Transition**	**Developing countries other than LDC's**	**Least Developed Countries (LDC's)**
eg: USA, UK, Australia etc	eg: Bulgaria, Hungary, Poland etc	eg: RSA, Botswana, Namibia etc	eg: Angola, Madagascar, Comores etc

Table 1.II : World Health Indicators, World Health Report 1998.

Country	IMR	Range IMR	MR u5	Range MR u5
Developed world overall	13	6 - 26	17	8 - 35
United Kingdom	6		7	
Australia	8		6	
Malaysia	11		21	
Mauritius	16		16	
Developing World overall	62	53 -100	83	68 - 144
Algeria	45		52	
South Africa	48		68	
India	73		90	
Zimbabwe	69		108	
Sierra Leone	172		251	

As can be seen, South Africa is grouped with the developing countries, but its health indicators are some of the best in this group. South Africa as a whole borders on being an "economy in transition", but within its borders many areas fit well into the definition of a developing country and some of the rural areas mimic the Least Developed Countries (LDCs).

Indicators used as a measure of perinatal health include maternal mortality rate (MMR), low birthweight rate (LBWR) and perinatal mortality rate (PNMR). In the developed world the maternal mortality is estimated to be about 27/100 000 live births with a range of 11- 62 (AbouZahr et al, 1996) whereas in the developing world this rate is far higher at 480/100 000 live births with a range of 140 - 1 060. The estimated MMR for South Africa is 150/100 000 live births (Pattinson and Moodley, 1998) although provincial studies such as that by Theron (1996) in the Cape Province indicate that MMR's vary enormously depending on the area studied. His estimate of MMR for the Cape Province was 38.1/100 000 live births (range 34,6 - 44,3/100 000 live births). At present in South Africa there is extensive research in progress with regard to MMR (Pattinson and Moodley, 1998) and a national drive to reduce this rate to more acceptable levels.

LBW and PNMR's in Africa are difficult to find. Airede et al (1995) estimate a LBWR in eastern and central Africa to be about 17%. This is similar to rates in South Africa. A global estimate of PNMR for Africa is not available. Published data by Louw et al (1995) give both LBWR and PNMR for the Cape Province of South Africa in 1991. Some of these rates are shown in Table 1.III. Comparative figures for the rest of the country are not published but are likely to reflect a similar range.

Table 1.III : Low birth weight rates and perinatal mortality rates for some areas of the Cape Province.

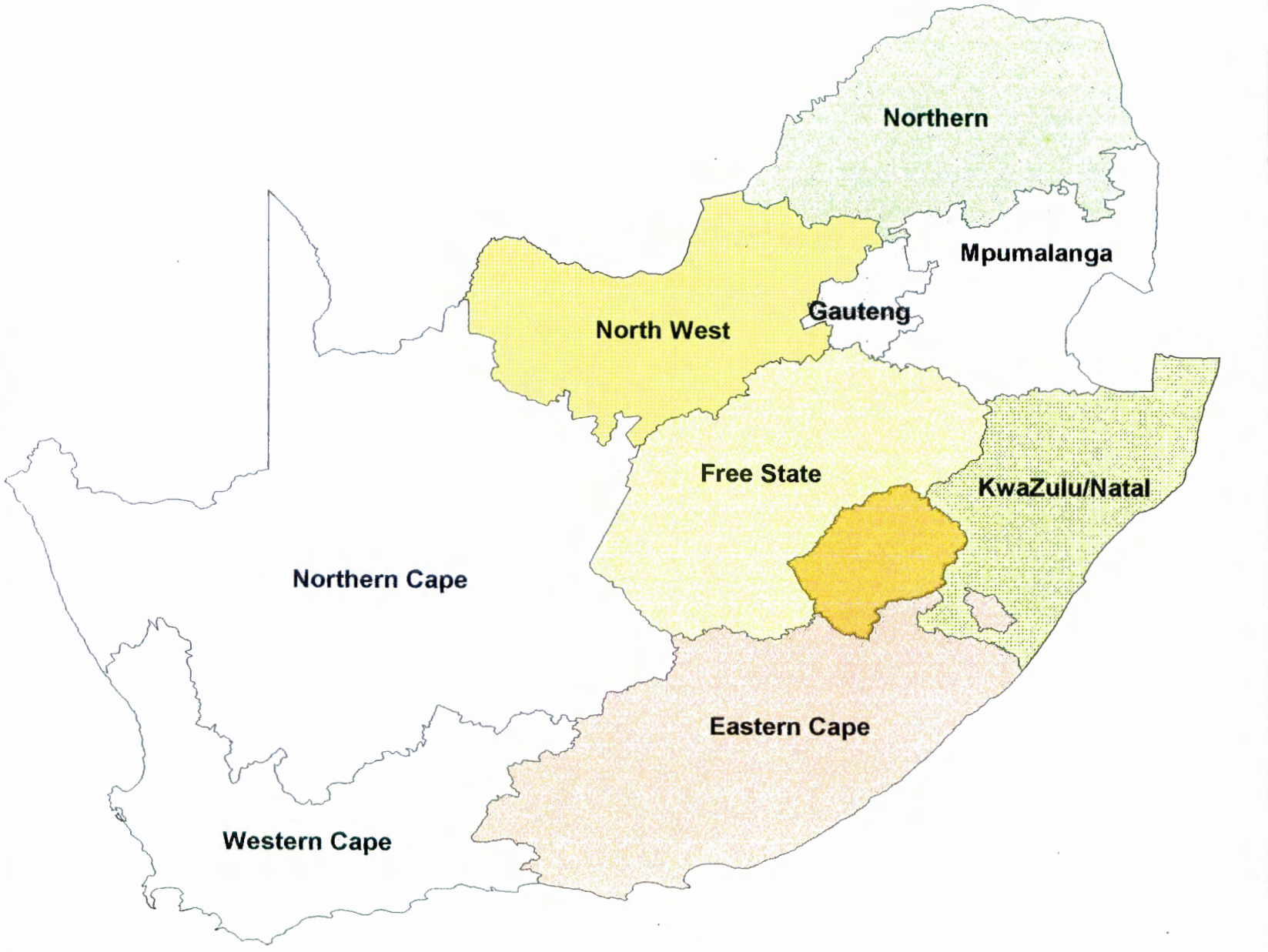
	LBWR	PNMR
North-Western Cape	24.8	27.43
Port Elizabeth - Uitenhage	13.2	40.33
Cape Town	13.9	19.18

It is clear, therefore, in the context of Africa as a developing continent, that South Africa is a country where the population is high, the IMR, MMR and MRu5 are, at best, 2-3 times that of the developed world. It is a country where at least 15% of infants weigh <2500g at birth and at least 2% of infants are stillborn or die in the first week of life.

South Africa finds itself in a unique position on the continent of Africa. Facilities characteristic of most developed countries are found in the major South African cities. At the same time, a burgeoning population with many people living in abject poverty exists on the fringes of the cities. Here people live largely in informal settlements where few basic amenities are provided. In the rural areas medical care is often lacking and transport to care inadequate. The coexistence of modern medical facilities with large disadvantaged communities creates particular problems as well as challenges.

Figure 1.1 South Africa and its provinces

(overleaf)



SOUTH AFRICA

N
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PROVINCIAL ADMINISTRATION WESTERN CAPE

Sub-Directorate
Information Management

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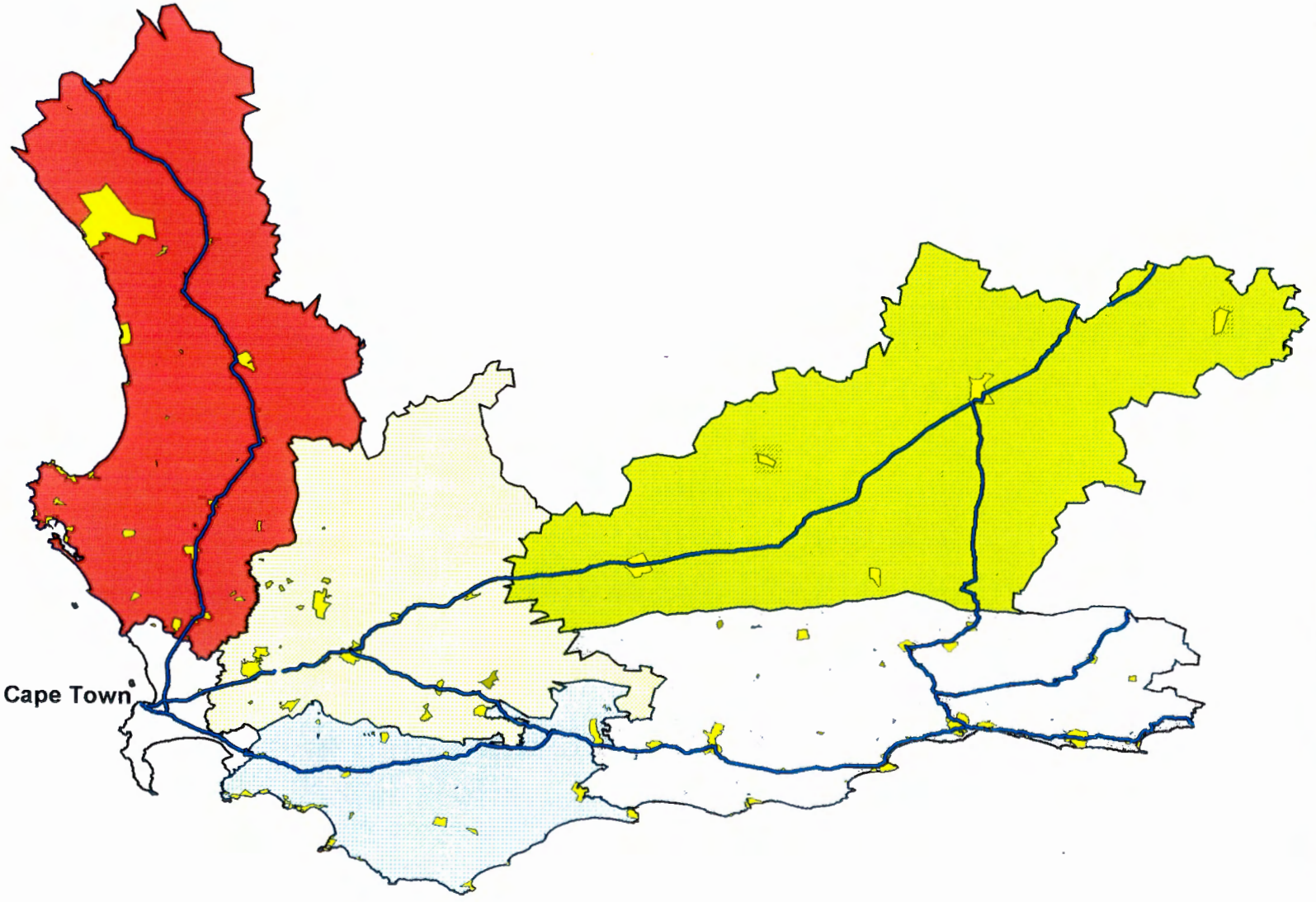
Figure 1.2 The Western Cape and health regions

(overleaf)



WESTERN CAPE PROVINCE

LEGEND

Roads
- National
- Towns

District Municipalities
- Cape Town
- DC1
- DC2
- DC3
- DC4
- DC5

N
W E
S

PROVINCIAL ADMINISTRATION WESTERN CAPE

Sub-Directorate
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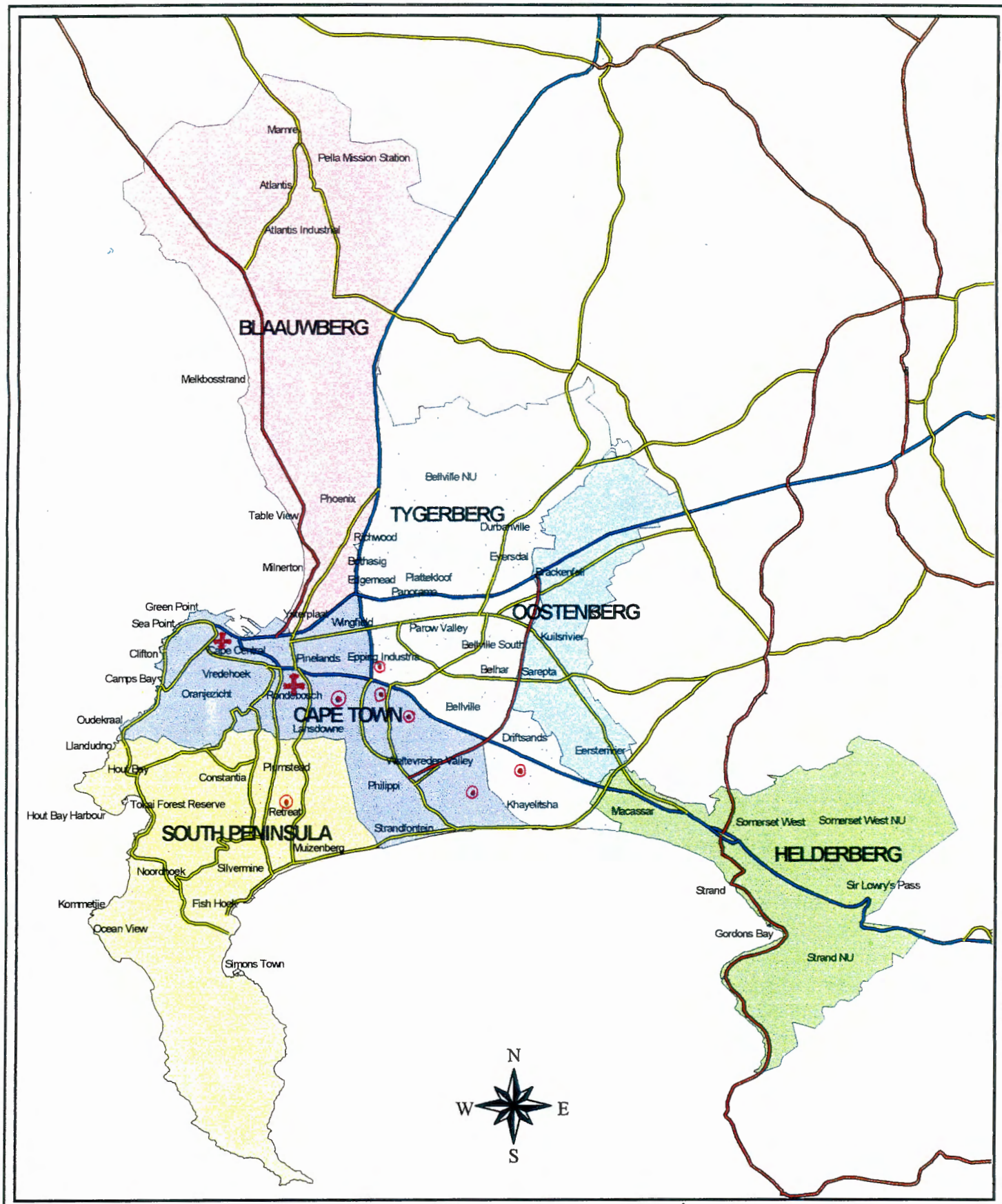
Figure 1.3 The Cape Town Metropolitan area with suburbs, hospitals and MOU's

(overleaf)

Additional legend:

The PMNS:	Symbol
Location of tertiary and secondary hospitals with ventilation facilities:	✠
Location of Midwife obstetric units (MOU's):	◎



LEGEND

Roads
- National
- Arterial
- Main

Substructures
- BLAAUWBERG
- CAPE TOWN
- HELDERBERG
- OOSTENBERG
- SOUTH PENINSULA
- TYGERBERG

WESTERN CAPE PROVINCE

Cape Metropolitan Area

PROVINCIAL ADMINISTRATION WESTERN CAPE

Sub-Directorate
Information Management

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There are nine provinces in South Africa (Figure 1.1). The Western Cape Province (Figure 1.2) has approximately 10% of the country's population. It is divided into four health regions - the Metropolitan, West Coast Winelands, Boland and Southern Cape/Karoo (boundaries not shown in Figure 1.2). The Metropolitan region is densely populated and contains two thirds of the population of the Cape Province, leaving the three rural regions with the remaining third. Both of the province's tertiary hospitals are situated in the metropolitan region. There are eight secondary hospitals, four of which are in the are in the metropolitan region and four in the outlying regions. Primary perinatal care facilities called Midwife Obstetric Units (MOU's) operate throughout the metropolitan region (Figure 1.3). Some secondary hospitals have neonatal units but only the tertiary hospitals and two of the secondary hospitals in the metropole can ventilate infants. Infants born outside of these four facilities, who require ventilation, are transported in to the nearest available facility.

Within the Metropolitan region, the facilities associated with the University of Cape Town are referred to as the Peninsula Maternal and Neonatal Service (PMNS). This service comprises seven MOU's, two secondary, and one tertiary hospital. The service delivers over 28 000 infants annually, roughly half in the MOU's and the rest in hospital. Neonatal follow-up services operate at all of the hospitals and also at MOU's by visiting doctors. Infants who are suspected of having disabilities are referred to a developmental clinic at the Red Cross Children's Hospital for further management and follow-up. The PMNS is responsible for care of patients without medical insurance. Those with medical insurance, who make up approximately 14% of the pregnant women in the Western Cape, are delivered in the private sector (personal communication, Mr Neil Gregory). The PMNS therefore caters for the less affluent section of the population. Figure 1.3 shows the suburban areas that form part of the PMNS and the location of the hospitals and MOU's in the network.

In order to appreciate the many problems within the PMNS, one needs to understand the nature of the population it serves. South Africa is a multiracial society with a chequered political past and a history of minority domination. Since 1994, democracy has been established but change is slow and much of the working and lower class peoples are still migrant workers. In the past many

of these workers were forced to live in the areas of the country formerly known as the Transkei and Ciskei (now part of the Eastern Cape Province) and by necessity had to travel to bigger centres such as Cape Town to seek work. This migration continues, despite the new democracy, and results in an antenatal population that is therefore vastly expanded by women who come to Cape Town in search of medical services. They usually arrive late in their pregnancies and many have little or no antenatal care. Most of them plan to return to their rural homes soon after the birth of the baby. As a result, complicated pregnancies and unhealthy new-borns are common and their follow-up is difficult as they often do not return for evaluation.

Several outcome studies over the years have emanated from Groote Schuur Hospital's Neonatal Intensive Care Unit (NICU). Collating all this data has become necessary due to the paucity of data and the need for information for planning for children's health care requirements. The all encompassing nature of the PMNS system allows for an easier and more accurate audit of neonatal outcome. Despite the limitations and the frustrations of working with a mobile population, the studies accomplished in the PMNS provide an acceptable assessment of the status of the high risk infant in Cape Town. This thesis embodies the bulk of research done over a ten year period in the NICU's and follow-up clinics of Groote Schuur and associated hospitals in Cape Town, South Africa.

Chapter 2

Aims

Three separate cohorts were selected and studied for this thesis with the following aims in mind:

1) To document neurodevelopmental outcome:

i) In the very low birthweight infant to six years of age.

ii) In the term infant post hypoxic ischaemic encephalopathy to three years of age.

2) To test methods for early neurodevelopmental screening

consisting of:

i) A risk rating score.

ii) The use of the Dubowitz Neurological Assessment.

iii) A numeric scoring system for the clinical evaluation of the severity of hypoxic ischaemic encephalopathy.

iv) The use of the Infant Neuromotor Assessment

These methods of newborn and infant screening will be evaluated for their predictive validity, sensitivity and specificity in terms of neurodevelopmental outcome (the presence or absence of cerebral palsy) at one year of age.

3) To propose a protocol for the follow-up of the high risk infant in the PMNS.

Chapter 3

Literature review

3.1 The high risk infant

Some infants are more prone then others to neonatal morbidity and mortality and to long term neurological disability. Since the birth of neonatal medicine in the early 20th century these infants have been recognised as "at risk" (Silverman, 1980). The term "high risk infant" is widely used in neonatology today. Nelson in his textbook defined it thus:

"The term "high-risk infant" designates infants who should be under close observation..."

In the context of this work, however, the term "high-risk" becomes more specific for those infants who are at risk for neurodevelopmental problems. This includes both infants of low birth weight and full term infants of normal birthweight who have experienced some brain insult which may predispose them to abnormal developmental patterns.

Many classifications of what constitutes the high-risk infant have been proposed. It is generally agreed that the infants at highest risk for neurodevelopmental problems are in two broad categories:

1) Low birthweight (LBW) and very low birthweight (VLBW) infants.

2) Term infants who show postnatal signs of hypoxic ischaemic encephalopathy (HIE).

This work focuses on these two categories of infants.

3.2 Prevalence of risk

3.2.1 The low birthweight infant

In order to discuss prevalence of risk it is necessary to define the risk categories so that published data can be accurately compared.

The low birthweight infant (LBW) is defined as an infant who's birthweight is less than 2500 grams. The very low birthweight (VLBW) infant has a birthweight less than 1500 grams. Only since the 1960's has it been appreciated that infants of low birthweight can be either preterm (<37 weeks gestational age) or growth restricted term (>37 weeks gestational age) infants or both. It becomes clear, therefore, that comparison of infant outcome and assessment of risk will vary depending on how infants are categorised. Assessment of gestational age can be difficult especially in countries where the menstrual history is often not known and where antenatal care inadequate. Dubowitz (Dubowitz et al, 1970) or Ballard (Ballard et al, 1979) scoring methods are often inaccurate in the more immature infant (Donovan et al, 1999).

Allocation of risk categories by birthweight is easier and allows for comparison between developed and developing countries. Standard accepted birthweight categories have already been defined in the preceding paragraph. While the LBW infant is at risk for neurodevelopmental problems, with the rapid evolution of neonatal care from the 1950's and since the publication of studies in the 1960's and 1970's it has become clear that VLBW infants constitute a much higher risk category and warrant closer attention.

The numbers of infants at risk varies world wide. In developed countries the incidence of LBW infants is lower than in developing countries. In the USA, according to Raju (1986), the prevalence of LBW is 6,8 % of all births and VLBW is about 0,6%, whereas in the Cape Province area of South Africa the LBW rate rises to 14,7% (Louw et al, 1995). There is no published data about VLBW rates in South Africa as a whole. In the city of Cape Town the rate is about 5% (unpublished statistics, neonatal department, Groote Schuur Hospital). There is a paucity of published data for the rest of Africa. The most recent data available is that quoted by Kinoti (1993) which gives a LBW rate for east, central and southern Africa which varies from 13 - 17%. Kinoti does not differentiate VLBW from LBW infants.

Studies in the eighties and nineties have repeatedly shown that infants of lower birthweight and gestational age are more at risk for developmental problems (Hack, 1993). Marlow et al in 1987 put forward strong evidence that the infants with a birthweight under 1250 grams were at highest risk and should receive the closest follow-up.

I have concentrated this literature review on the infant with birthweight less than 1500 grams.

3.2.2 Factors that affect the outcome of the VLBW infant

Other than birthweight and gestational age, there are multiple factors that influence the outcome of the VLBW infant. Many studies have aimed to identify perinatal and postnatal variables that correlate with morbidity, mortality and neurodevelopmental outcome (Tarnow-Mordi et al, 1990; Ornstein et al, 1991; Marlow et al, 1993; to mention but a few). The comprehensive review by Bregman in 1998 not only reviews the neurodevelopmental status of the VLBW infant but addresses the issue of morbidity and influencing factors, as well as what factors have been shown to have a positive effect on outcome at all levels. There are few factors that have consistently been shown to correlate directly with outcome.

Mortality and morbidity

Surfactant therapy has been identified in the developed world as a key factor in the improved survival of the VLBW infant (Bregman, 1998) in the 1990's. Antenatal steroid administration has also ensured better quality survival of the less mature infant and even in Africa, where surfactant is largely unaffordable, this has been a feasible treatment modality to improve survival (Cooper et al, 1999).

Neurodevelopmental outcome

Two factors stand out in most studies as important determinants of neurodevelopmental integrity. These are: The presence of intraventricular haemorrhage or periventricular white matter damage; and the influence of the socio-economic status of the family.

Intraventricular haemorrhage (Volpe, 1989) is associated both with increased mortality and morbidity in the infant. Larger haemorrhages with extension into the ventricular system, with or without cerebral parenchymal involvement, have been shown to be associated with abnormal neurodevelopment (Vohr et al, 1992; Levene and de Vries, 1995). Infants with grade III or IV haemorrhages (Levene and De Cresigny, 1983) are therefore at high risk.

Periventricular white matter injury consists of either cystic periventricular leucomalacia (PVL) or intraparenchymal white matter haemorrhage associated with ipsilateral periventricular-intraventricular haemorrhage (PV-IVH). PV-IVH occurs in about 10-15% of extremely low birthweight (ELBW) and PVL in 3-4 % of VLBW infants in developed countries (Perlman, 1998).

It has been shown to occur in up to 50% of VLBW infants in Africa (Sandler et al, 1994). There are multiple perinatal events associated with the development of PVL or PV-IVH which makes prevention complex. Both these white matter lesions are associated with poor neurodevelopmental outcome including cerebral palsy (CP) and cognitive deficits. The size of the lesion has some correlation with outcome and some infants with very small lesions may not show signs of CP but have been shown to have lower cognitive abilities at 5 years of age and older (Fawer and Calame, 1991; Vohr et al, 1992).

Socio-economic status has consistently been shown to correlate with outcome in the VLBW infant (Ornstein et al, 1991). Across the world poor neurodevelopmental outcome is associated with poverty and low parental education levels (Marlow et al, 1987; Bregman, 1998; Vohr et al, 1992; Molteno et al, 1991)

3.2.3 The underweight for gestational age (UGA) infant

The term underweight for gestational age is defined as the infant who has a birth weight equal to or less than the tenth centile expected for gestational age (Lubchenco et al, 1966). These infants may be grouped into two categories: the infants who are symmetrically stunted where head circumference is proportional to weight and length, and the asymmetrically stunted infants where head circumference and length is spared. The presence of growth restriction is more common in some geographical areas and in certain population groups. The Western Cape area of South Africa is renowned for its population of mixed racial origin where the mothers commonly have infants of low birthweight (Malan et al, 1967) and have been found by Woods et al (1978) to be significantly shorter, lighter and thinner than the mothers in this area who are of European origin. The infants of these mothers have been found to be light and short but with some head sparing and normal weight/length proportions (Woods et al, 1981). It has been postulated by the same authors that these infants characteristically are born to underweight mothers and that the mothers themselves are symmetrically stunted in response to nutritional stress and may be adapted to a life of reduced caloric intake.

The influence of restricted intra-uterine growth on outcome is not completely clear. In some studies the UGA infants have less cerebral palsy and more normal outcome than appropriately grown infants but others have shown that in the long term the UGA infants have significantly

lower intellectual function and predisposition to learning problems. A group of UGA South African infants was followed by Molteno et al (1995) to five years of age but were not found to score significantly less than their well grown controls on global developmental assessment although they had less well developed language skills.

A recent comprehensive review (Goldenberg et al, 1998) presents key findings of many of the major studies of UGA infants. The authors conclude that cerebral palsy is rarely found in UGA preterm infants but that UGA term infants are at increased risk for CP. This apparent contradiction is closely related to the fact that term UGA infants who are asymmetrically grown are far more likely to suffer from perinatal hypoxia. This review also makes it clear that growth restricted infants of any gestational age are without doubt at increased risk, by school entry, for minor neurological dysfunction, school failure and attention deficit hyperactivity disorder.

3.2.4 Outcome of the VLBW infant

The neurodevelopmental outcome of the VLBW infant has been well documented for developed countries over the past 40 years. However, in developing countries published literature is sparse and confined mostly to South African studies. For the sake of clarity the relevant literature has been discussed separately. For developing countries this survey has been based in Africa only.

a) Outcome of the VLBW infant in the developed world

For review of the literature until the end of the nineteen eighties, one key article summarises the main findings over three decades. Escobar et al (1991) reviewed articles from 1960 - 1988. His extensive meta- analysis covering 11 studies and over 20 000 VLBW births showed a mean incidence of cerebral palsy in infants <1500 g of 7,7% and an overall disability of 25%. There was no improvement in incidence of disability over time and notably no increase in incidence despite improving survival rates. His outcome measure of overall disability encompassed cerebral palsy as well as intellectual disability, visual and auditory impairment and also included disability related to medical morbidity e.g. severe chronic lung disease. This meta-analysis did not demonstrate an increased rate of disability or CP in infants with birthweight less than 1000 grams (extremely low birth weight (ELBW)) compared to those between 1000 and 1500 grams but he found the relative risk of CP in VLBW infants was increased 38 times over the general population.

Two further review studies looked at outcome in the 1980s. Aylward et al (1989) looked at 80 studies between 1979 and 1989 involving LBW infants. The total number of infants reviewed was 4006 index and 1568 controls. Aylward et al looked mainly at intelligence quotients (IQ) and developmental quotients (DQ) at final assessment at ages between 2 - 10 years. He found the VLBW child to score significantly less well than the control. In the group of studies he analysed that had control groups the abnormality rate in index and control children were 14% and <1% respectively. Ornstein et al (1989) looked at 25 studies of VLBW infants published since 1980, all of which followed the children for 5 years or longer. The same conclusions were reached: VLBW children without CP or major disability have IQ scores within the normal range but have an increased need for special education and remediation. They have increased behavioural problems, and a greater incidence of fine and gross motor incoordination compared to term controls. Females generally fare better than males. There is a growing consensus that despite normal IQ as many as 50% of all VLBW children will underachieve at school (Ornstein et al, 1991; Hack and Fanaroff, 1999).

In the 1990s most literature concerned the infant with a birthweight less than 1000 grams. Survival rates of these small infants have improved from less than 10% in the 1960's to more than 70% in the 1980's (Bregman, 1998). With the survival of more immature infants has come an unfortunate rise in both the prevalence and severity of disability with the emergence of more multiply disabled infants (Hagberg, 1989). A recent review by Hack et al (1999) looks exclusively at ELBW survivors with birthweights less than 800 grams and gestational ages less than 26 weeks. Neonatal intensive care has progressed to a point where the limits of viability have been extended to the 23 and 24 week infant. Again associated with the survival of these extremely tiny and immature infants is a high percentage of neonatal and infant morbidity and neurodevelopmental disability.

Table 3.I : Comparison of outcome of ELBW infants (<800 g and <26 weeks) over two time intervals (Hack et al, 1999)

	1990 - 1992	1993 - 1995
20 month survival rate	43%	38%
Chronic lung disease	41%	63%
Abnormal cognitive function	20%	48%
Cerebral palsy	10%	16%

The key outcome measures as stated by Hack et al are summarised in table 3.I. Despite a similar survival rate over two time periods there was a disturbing increase in both medical and neurological morbidity. Hack concludes that " with current methods of care, the limits of viability have been reached. The continuing toll of major neonatal morbidity and neurodevelopmental handicap are of serious concern". The developed world are now more concerned that advances in neonatal intensive care may in fact be detrimental to outcome and that we may now begin to see iatrogenic effects of this care in the extremely immature survivor as they reach late childhood and adulthood. Hack suggests that we may become aware of an epidemic of abnormality similar to the discovery of retrolental fibroplasia caused by the liberal use of oxygen therapy in larger birthweight infants in the 1950's.

b) Outcome of the VLBW infant in Africa

The situation in the developing world reflects that of the developed world 20 years ago. The lower limits of viability remain around 27-28 weeks of age and birthweight 700 -800 grams as the extremely low birthweight infant is less likely to be offered ventilation. The developing world continues to struggle with scant resources and access to adequate health care remains the major limiting factor for improved outcome.

Published literature emanates from the major centres where resources do exist for neonatal intensive care. Most of these tertiary centres reflect outcomes approximating the developed

world, although the ELBW survivor is largely absent from these reports. The majority of comprehensive reports in Africa are South African studies (Table 3.II).

The earliest published follow-up study by Molteno et al (1976), from Groote Schuur Hospital NICU, followed 86 VLBW infants (birthweights ranged from 500 - 1500 g). He looked at survival, growth and neurodevelopmental outcome at one year of age. Overall survival was 69% with 6% having CP and 4 % developmental delay.

Ballot et al (1992) completed a retrospective follow-up study which describes outcome between one and three years of age in a cohort of ventilated LBW NICU survivors from Johannesburg Hospital. This study concentrates on speech and hearing problems and found a high correlation between abnormal or delayed speech and neurodevelopmental problems in the infants.

Thompson et al (1993) published the outcome of infants less than 1250 g birthweight from Groote Schuur Hospital, Cape Town. This data is presented in detail in chapter 4 of this thesis. Some of the main outcome findings are summarised in Table 3.II.

Kirsten et al from Tygerberg Hospital, Cape Town (1995) followed 117 of 153 ventilated VLBW infants for one year. Almost twelve percent of these infants had CP. They found an increased incidence of disability in infants with birthweights under 1000 g. They comment only on the incidence of cerebral palsy while intellectual function was not reported. The sample studied was a cohort selected from the sickest infants in their NICU. Morbidity rates for BPD, ROP and deafness were as quoted in Table 3.II.

Cooper et al in Johannesburg (1997) followed 86 of 113 enrolled VLBW infants to 18 months of age. The cohort was divided into 3 groups:

Group 1: Ventilated, birthweight >1000g

Group 2: Not ventilated, birthweight >1000g

Group 3: Birthweight <1000g

They reported a survival rate of 66% for infants 1000g - 1499 g and 24% for infants <1000 g. A little over 10% of these survivors were disabled (CP, Bayley score <70, blindness or deafness). The majority of disabled infants (eight of ten) were from group 1.

Table 3.II : Comparison of South African studies of LBW infant outcome

Study (year)	Study type	Outcome measures	Results
Molteno et al (1976)	Prospective VLBW 500-1500 g n = 86	Survival, growth and neurodevelopment to 1 year	SR 69% CP 6% Dev delay 4 %
Ballot et al (1992)	Retrospective Ventilated NICU LBW survivors n = 83	Neurodevelopment (ND), speech and hearing (S & H) 1 - 3 years of age	High correlation of S & H problems with ND abnormalities
Thompson et al (1993)	Prospective cohort study. BW <1250 g Control group @ 6 years. n = 96	Survival , morbidity and neurodevelopment at 1, 2 and 6 years	SR >1000g: 81 % SR <1000g: 42 % CP rate: 6% ID rate without CP:5% Controls: no ID or CP
Sandler et el (1994)	Prospective prevalence study LBW n = 282	PVH and outcome to hospital discharge	IVH <1500 g and <32 weeks: 53% Grade III and IV IVH: 12% SR: 81%
Kirsten et al (1995)	Prospective Ventilated LBW n = 153	Survival, morbidity and CP rate at 1 year	CP: 12 % BPD: 19% ROP (gr 3 & 4): 7 % Deafness: 2.6%
Ballot et al (1996)	Prospective 1001 - 1500 g & < 31 weeks n = 231	CRIB score evaluation. Death, IVH and CLD incidence to hospital discharge	Correlates with poor outcome: Birthweight Lowest FiO2 Maximum PaCO2
Cooper et al (1997)	Prospective Stratified sample VLBW n = 113	Growth and ND up to 18 months.	SR 1000-1500g: 66% SR <1000g: 24% CP: 11% Increased rate CP in BW < 1000 g

No long term studies assessing neurodevelopmental outcome of LBW or VLBW infants are reported from elsewhere in Africa. Further studies from South Africa are short-term and are mainly morbidity and mortality studies.

Sandler et al (1994) studied periventricular leucomalacia in LBW infants at Baragwanath Hospital but outcome was only reported until hospital discharge. The overall survival rate was 81% and IVH rate was 53%. Ballot et al (1996) evaluated predictors of poor early outcome (i.e. death, intraventricular haemorrhage and chronic lung disease) using the Clinical Risk Index for Babies (CRIB) score and other intensive care criteria. She found that the full CRIB score was not predictive of death or impairment but that the lowest, earliest required inspired oxygen concentration and highest arterial carbon dioxide concentration and birthweight could be correlated with outcome.

The relative lack of available published data on long-term outcome is a reflection of the difficulty in obtaining adequate follow-up in the developing world. This poor follow-up rate is a result of many factors but includes transport difficulties in rural populations, financial constraints and too few medical personnel who are able to indulge in time consuming follow-up work.

3.2.5 Birth asphyxia and HIE

In order to report on the prevalence of risk for these infants, the definition of the terms used is necessary:

Hypoxia or *anoxia* is the partial or complete lack of oxygen in one or more tissues of the body. This is related to hypoxaemia and results in a metabolic acidosis due to lactic acid accumulation. Hypoxia can occur prior to, or during birth and is often called perinatal asphyxia.

Ischaemia is a reduction in, or cessation of, blood flow that arises from either systemic hypotension or occlusive vascular disease (Vannucci, 1992).

Hypoxic ischaemic encephalopathy refers to the post-natal clinical neurological sequelae resulting from the deprivation of oxygen to the brain due to the combined effects of hypoxaemia and ischaemia.

Asphyxia Neonatorum (birth asphyxia) is the failure of the newborn infant to establish adequate respiration at birth. (Donald, 1959)

In order to report on risk prevalence and to compare literature reports from different centres, ideally the criteria for birth asphyxia and HIE should be standard. Finding such a standard is

however, extremely difficult. As a result, many differing criteria have been used world wide which makes comparison between studies difficult. Most frequently, criteria for the diagnosis of birth asphyxia have been defined in terms of Apgar scores. But it is well known that there may be little correlation between Apgar score and signs of perinatal hypoxia (Nelson et al, 1981; Levene et al, 1986; Carter et al, 1993). Studies reporting asphyxia rates often use differing Apgar scores to identify the cohort for inclusion. Some studies use a five minute Apgar score of less than and equal to six, others use a more stringent criterion of less than three. Therefore, meaningful comparison of asphyxia rates from different centres is often impossible. The use of umbilical cord blood acid-base status may be a more accurate reflection of hypoxia but has also been shown to have a poor correlation with signs of birth asphyxia (Carter et al, 1993). Carter et al also make the point that the degree of acidosis indicating hypoxia is unclear. However, for want of a better quantifiable parameter, these two measurements are commonly used in the literature to assess the incidence of perinatal hypoxia in any one population.

As with the incidence of preterm and VLBW infants, the incidence of birth asphyxia is higher in developing than developed countries. For birth asphyxia in term infants, the incidence in first world reports varies from 2.9 to 9.0 per 1000 live births (Levene, 1995) whereas in Africa the limited data published indicates an incidence of 210 cases per 1000 live births (Kinoti, 1993). This extremely high incidence must be viewed with circumspection as the criteria used for the diagnosis of asphyxia in Kinoti's study was an Apgar score less than seven at five minutes, whereas in the quoted first world reports acid base status as well as perinatal diagnostic criteria such as abnormal cardiotocograph tracings prior to delivery were also considered when the diagnosis of asphyxia was made. Nathoo et al (1990) from Harare, Zimbabwe, report an incidence of asphyxia from the urban centre of Harare of 15/1000 live births. They have used more stringent criteria than Kinoti to define asphyxia (five minute Apgar score of five or less). Molteno and Arens (1996) in a review of the causes of cerebral palsy in Cape Town showed that birth asphyxia is still a major cause of CP in the black population group here.

In the academic centres of South Africa asphyxia rates are similar to first world reports:

Gregersen at al (1999), Johannesburg	6.0/1000 live births
Hall et al (1994), Tygerberg (unpublished)	4.6/1000 live births.

Saloojee et al (1993), Baragwanath (unpublished)	6.7/1000 live births.
Adikhari et al (1992), Durban (unpublished)	3.3/1000 live births

Infants who suffer from birth asphyxia may or may not deteriorate postnatally and show clinical signs of HIE. The term HIE was postulated as a descriptive term for the mechanism of brain injury in hypoxic infants by Volpe (1976). Since his early description of this neurological condition in the neonate the term HIE has become widely used. HIE, being a clinical postnatal diagnosis, is more easily defined and has been graded in terms of severity by Sarnat (1976) and modified by Fenichel (1983). Fenichel's grading system is widely used in the assessment of severity of HIE and evaluation of prognosis. The incidence of the condition world wide has been evaluated using this grading system (Levene, 1995; Hull, 1992; Airede, 1991). Infants with grade I HIE are mildly affected whereas those with grade III HIE have suffered a severe hypoxic insult.

In a Nigerian urban centre the incidence of HIE was 26/1000 live births (Airede, 1991) which is far higher than the incidence of 6/1000 live births reported for the developed world (Levene, 1995). In Nathoo's Zimbabwean study the HIE rate was 11/1000 live births (Nathoo et al, 1990).

South African academic centres again have rates equivalent to the developed world:

Saloojee et al (1993), Baragwanath (unpublished)	3.4/1000 live births.
Gregersen et al (1999), Johannesburg	4.6/1000 live births

3.2.6 Outcome of the infant with HIE

a) Outcome of the infant with HIE in the developed world

A key review by Robertson et al in 1993 states that "Available evidence shows that adverse sequelae do not follow perinatal asphyxia unless encephalopathy is part of the neonatal clinical presentation." Literature reviewed is that which deals specifically with those infants who have clinical signs of HIE.

It is widely accepted that the infant with severe HIE (Sarnat Grade III) has a universally poor outcome of either death or disability. Levene (1995) indicates CP rates of 100% in survivors, 40-50% in grade II HIE and less than 5% in grade I. The majority of these abnormal infants have

severe neurodevelopmental disability, namely spastic quadriplegia with intellectual disability. Often multiple disability is present with blindness and deafness.

Robertson and Finer in their review in Clinics in Perinatology, June 1993, showed a better outcome overall in 174 children with HIE over an 8 year period in the moderate (grade II) group:

Mild HIE:	all normal
Moderate HIE:	80% normal, 15% disabled, 5% dead
Severe HIE:	Nil normal, 18% disabled, 82% dead

The overall risk of death for children with all stages of HIE combined was 12.5%, neurologic disability 14.3% and death or disability 25%. Later follow - up to 8 years of age of the "normal" children in the moderate group showed an increase in learning disability from 20% in a control group to 36% in the HIE group.

More recent data on neonatal encephalopathy (Naqeeb et al 1999) assesses the amplitude-integrated electroencephalogram (aEEG) as a method of early evaluation and correlates this with neurodevelopmental outcome. In Naqeeb's study, however, the cohort included infants with non-asphyxia related encephalopathy and the outcome for infants with HIE is not given separately. Toet et al (1999) has also evaluated the aEEG and has assessed outcome. Of the 68 infants included in the cohort only 35 (52%) were normal. Twenty one infants (31%) died and 11 infants (16%) were disabled. Eighteen of the 21 deaths were classified as grade III encephalopathy and three were grade II encephalopathy.

b) Outcome of the infant with HIE in Africa

Publications on the outcome of HIE in Africa are few. The increased incidence of birth asphyxia and, therefore, HIE is a cause for concern and has resulted in a some published works, although all reporting short term outcome only.

A comprehensive review by Costello and Manandhar in 1994 indicates that HIE is a major contributor to perinatal mortality in the developing world and that HIE and birth asphyxia are likely to both be significant contributors to abnormal neurodevelopmental outcome. But, as these

authors state, no studies proving this hypothesis had been published from developing countries prior to 1994.

The only published African follow-up study found was that of Gregersen et al (1999) from Johannesburg. They reviewed birth asphyxia and CP rates from the Johannesburg Hospital. They attempted to assess the preventability of CP by reviewing labour and delivery details of 48 asphyxiated infants. The follow-up rates were poor (27 infants or 56% of the cohort were evaluated) and the age to follow-up was not stated. They concluded that 46% of the cases of birth asphyxia were preventable. Forty eight percent of the infants followed were abnormal and 12,5 % died. Again, all the abnormal infants had either grade II or grade III encephalopathy and 60% of the infants in the grade III group died. Their conclusions state that their CP rate following birth asphyxia is three times that of the developed world and that many of these cases are preventable.

Most other literature reviewed dealt with early outcome and did not constitute prevalence studies. Longer term follow-up studies have been found in conference proceedings and are, as yet not published.

Illiff et al (1994) from Harare Maternity Hospital (Zimbabwe) followed 159 infants of a cohort of asphyxiated term infants together with 143 controls. He followed the infants to 18 months of age and reported a 21% abnormality rate in infants with HIE and a 3% abnormality rate in controls. Thirty-eight percent of the original HIE cohort died prior to hospital discharge. He also reviewed mothers' folders and demonstrated a significantly higher incidence of prolonged labour in the mothers' of affected infants.

Saloojee et al (1994) from Johannesburg, studied prospectively all term asphyxiated infants born at or referred to Baragwanath Hospital over a one year period. The survivors were followed until one year of age when they were assessed on the Bayley scales of Infant Development (Bayley, 1969). Seventy-four percent of survivors (53 infants) were seen at one year of whom 45% had CP and, again, all these infants had had grade II or III HIE. Multiple disabilities were found in the infants with CP with 50% having seizures and 13% having severe visual impairment.

Thompson et al (1995) have assessed outcome to one years of age in a cohort of infants with HIE in Cape Town and this cohort has now been followed to three years of age and is presented in chapter 5 of this thesis.

The glaring lack of data from Africa, despite the knowledge that perinatal hypoxia is a more significant problem than in the developed world, should form the impetus for co-ordinated, multi-centre long term follow-up studies as soon as possible.

3.3 The importance of follow-up

The need for follow-up of the high risk infant has been highlighted since the emergence of the first studies in the 1950's. The use of audit in evaluating the effects of neonatal intensive care has become a necessity. William Silverman in his historical perspective (1980) tells the story of the emergence of retrolental fibroplasia as a clinical entity and illustrates how it taught the clinician that assessment of outcome can modify care practices for the benefit of the child. Since then a host of literature expounds the merits of follow-up and emphasises the need for long-term follow-up. Keily et al in 1981 set down suggested guide lines for follow-up of the LBW infant. He included several criteria that should be fulfilled: the impartiality of the observer; 100% follow-up of the cohort; and long-term follow-up, preferably to school age. He also emphasised the importance of the use of controls. The value of long-term follow-up has been borne out by studies in the late1980s and early 1990s which published outcome results of VLBW and high risk term cohorts of school-going children, and illustrated the impact of increased learning disabilities (Ornstein et al 1991, Collin et al 1991, Saigal et al 1991, Robertson et al, 1989). In Africa, there are no published studies looking at school performance in children who had high risk births, either preterm or term.

Few studies, even in the developed world, have managed to achieve 100% follow-up. The British study by Wariyar et al (1989) clearly showed that infants who were difficult to trace had a higher percentage of disabilities. He suggested that parents who have not come to terms with their child's disability will avoid medical contact. This opinion is also held by Keily et al (1981) who suggest that two trends in follow-up of an incomplete cohort exist: Those that reflect excess disability because parents of disabled children seek attention; and those where parents in denial avoid contact resulting in an underestimate of the true disability rate.

3.4 The Neurodevelopmental evaluation

Because the neurological system of the infant and young child is so dynamic, clinical neurological assessment which is appropriate for the adult and adolescent is not applicable to the younger child. Neurological assessment must encompass a neurodevelopmental approach. For each age and stage of development a specific method of evaluation is required.

3.4.1 History

There have been several groups of distinguished neurologists and neurodevelopmentalists who, over the past 40 years, have described many methods of assessing the neurological and neurobehavioural status of infants and young children. The first of these was Andre-Thomas et al in 1960. Their work was closely followed by that of Beintema (1968), Touwen (1976), Sante-Anne Dargassies (1977), Prechtl (1977), Amiel-Tison (1968). By the 1980's neurological assessment of the newborn had become more refined and several researchers in the field of newborn development published assessments in the pursuit of the ideal evaluation which would both diagnose abnormality and detect those infants who required closer follow-up after hospital discharge. The first of these was Dubowitz (1981) closely followed by Brazelton in 1984 and Capute in the same year. Amiel-Tison continued her work in the field and published her findings in 1986 and more recently in 1999. By the late 1980s and early 1990s when resource constraints began to affect services even in developed countries, the emphasis changed to publishing assessments which would identify, as early as possible, high-risk infants most in need of follow-up. At this time a number of early infant screening tests were developed by Allen et al (1997), Magasiner et al (1997) and others.

3.4.2 Types of neurodevelopmental assessment

a) Assessment of the newborn

According to Volpe (1995) the neonatal neurological examination assesses the intactness and maturity of the central nervous system. A recent review by Majnemer et al (1998) closely examines nine frequently used newborn assessments. Those chosen include only assessments

applied to the newborn and infant under one year of age and exclude those by Andre-Thomas (1960) and Saint-Anne Dargassies (1974).

All nine assessments are evaluated for reliability and validity. Their conclusion states that most assessments are very similar and none stand alone. Neurological evaluation of the newborn must also involve special investigation and general clinical impression.

In the developing world the emphasis, even more than the developed world, must be to screen high risk infants as soon as possible so as to reduce the load on already overwhelmed resources. If this can be done in the NICU prior to discharge, much time and many resources can be saved. Given the number of patients to be seen and the staff constraints, the newborn evaluation must take a reasonably short time to be administered, without the examiner requiring special training. It should also be a good prognostic tool. The assessment also should be useful if special investigations such as cranial ultrasound are not available, as is often the case in developing countries.

b) Evaluation of the newborn with HIE

The most widely used classification of HIE is that of Sarnat and Sarnat (1976) which groups affected infants into one of three categories: Mild; moderate; and severe. The decision as to whether an infant falls into the moderate or severe category is at times difficult. Application of this grading system is also time consuming and requires some paediatric expertise as well as availability of electroencephalographic evaluation of the infant.

More recently three published studies have developed numeric scores for HIE. Portman et al (1990) developed a score that predicts early morbidity and mortality. Two other papers developed scores which have been related to long-term outcome; Lipper et al (1986) used the post asphyxia score and Bao et al (1993) a neonatal behavioural neurological assessment. These latter methods are time consuming, involving 17 or more measures and require some training. Both, however, have found value in the use of such scores to predict neurodevelopmental outcome.

The use of the amplitude integrated EEG (aEEG) in the newborn was described by Svenningsen in 1990. He demonstrated the differing wave patterns in fullterm and preterm infants as well as pattern changes occurring with illness, seizures and medications. He went on to define abnormal wave patterns as seen in varying neonatal conditions. As a follow-up to this work Hellstrom-Westas et al (1995) went on to assess the use of the aEEG in the evaluation of the asphyxiated term newborn and its predictive value with regard to outcome. They were able to evaluate the infants within the first six hours of birth and some as early as three hours after birth. aEEG was correlated with conventional EEG. They found a normal aEEG to be highly predictive of normal outcome (PPV 96.2%) and that it was as useful as EEG (PPV 95.6%). Even the abnormal aEEG was predictive of abnormal outcome although a little less so (PPV 85.7%). The aEEG was less accurate at three hours of age as in a small proportion of infants an abnormal pattern reverted to normality between three and six hours. This work has now been revisited by Naqeep et al (1999) and Toet et al (1999). Naqeep et al used the aEEG in a cohort of 56 infants with neonatal encephalopathy. In 16 of the 56 infants the cause of the neonatal encephalopathy was not hypoxia. The authors sought to define normal aEEG patterns in all these infants and to assess its predictive value for outcome. They also evaluated inter-observer reliability with the aEEG and correlated it with EEG and magnetic resonance imaging. The aEEG was again shown to be useful and highly predictive. Toet et al re-evaluated the aEEG at 3 and 6 hours after birth in a cohort of 68 infants with HIE. He found it to be predictive even at 3 hours of age and postulated that it could be used for assessment of the encephalopathic newborns for rescue therapy following hypoxia.

Despite the fact that there are now very accurate and early means of assessing the encephalopathic newborn none of these modalities are readily available in Africa. Reliance must still be placed on clinical methods of assessment.

c) Early infant assessment

In early infancy rapid maturational changes necessitate neurological assessment to be dynamic and to encompass a neurodevelopmental approach. The vast majority of infant assessments, reflecting the predominant stage of development of the infant uder 12 months of age, are motor

assessments. At this age, evaluation must detect CP early and should enable the examiner to label other infants who are at higher risk for more subtle forms of CP and other later disabilities.

Included in the most commonly used early infant neuromotor assessments are the Milani-Comparretti Motor Development Screening Test (MC) (Milani-Comparetti and Gidoni, 1967), the Chandler Movement Assessment of Infants Screening Test (CMAI-ST) (Chandler, 1986), The Infant Motor Screen (IMS) (Nickel et al, 1989), The Infant Neurological International Battery (INFANIB) (Ellison, 1994) and the Alberta Infant Motor Scale (AIMS) (Piper and Durrah, 1994). Some, such as the AIMS, are time consuming to administer and all, except for the CMAI-ST, use global scoring which is cumbersome to apply in a busy clinic (Magasiner et al, 1997).

A recent publication by Haataja et al (1999) proposes a neurological examination for infants from 2 months to 24 months of age. It is developed from several other infant examinations and incorporates neurological examination, assessment of posture, movements, tone, reflexes and reactions as well as behaviour. The end point is a global optimality score. The use of this score enhances the usefulness of the examination and allows for easy statistical analysis and correlation of outcome with imaging and electrophysiological findings, both in a clinical and research setting. The assessment is, however, very long and scoring certainly time consuming.

The developing world needs an assessment that is quick, easy and predictive and the Infant Neuromotor Assessment (INA) has been developed for this purpose and has been shown by Magasiner et al (1997) to fulfil all these criteria.

d) Later neurodevelopmental evaluation

From one year of age other aspects of neurological function must be evaluated more fully. Cognitive tests and more comprehensive developmental evaluation become necessary. Ideally the vast majority of infants with CP should have been detected by one year of age. After this age the neurodevelopmental assessment aims to detect cognitive disability and more subtle forms of CP. There are several comprehensive assessments from which to choose.

The Bayley Scales of Infant Development (Bayley, 1969) consist of two scales which can be applied from early infancy until three years of age. In infants under a year the score comprises mainly motor items and after one year psychomotor items are added. After one year of age both

components constitute the score which is called the Bayley Mental Index. From the second year of life this index begins to approach a measure of infant intelligence. These scales place less emphasis on language and are popular in the United States of America having been standardised for that population. The Bayley Scales are useful in identifying normal and obviously abnormal infants but are limited in their ability to detect the infant with suspect or borderline function (Harris et al, 1994).

The Griffiths Scales of Mental Development (Griffiths, 1976) are applicable from infancy through to eight years of age. Other available assessments are modified IQ tests and include the Catell Infant Intelligence Test, the McCarthy Scales and others. The Griffiths Scales were developed and have been standardised in Britain. They have been adapted for use in the developing world but as yet are unstandardised for the South African population.

3.4.3 The Griffiths' Scales

This neurodevelopmental assessment has been widely used mainly in European and Australian studies (Marlow et al, 1987; Aylward et al, 1989;Fawer and Calame, 1991; Bowen et al,1996). These scales are divided into six subscales: Locomotor; personal and social; hearing and speech; eye and hand; performance and practical reasoning. The last scale becomes applicable from the second year. This assessment encompasses all areas of development. Language ability forms an integral part. It has been shown to have a good correlation with later IQ especially after two years of age and to be sufficiently sensitive to identify those high-risk children with borderline intellectual function who are likely to have later school learning problems (Bowen et al, 1996). It can be used from infancy but, according to Bowen et al, detection of minor problems becomes more accurate from about three years of age. It is a little less accurate in detecting visuo-motor problems at this age.

Use of the Griffiths' Scales in South Africa.

A local standardised measure of intelligence was developed in South Africa and published in 1981 (EM Madge). The Junior South African Intelligence Scales (JSAIS) are widely used with pre-schoolers and are applicable between the ages of three and eight years of age. The disadvantages of the JSAIS are that the scales cannot be used under three years of age and

there is no measure of locomotor or personal-social development. The extended Griffiths' Scales (for 2-8 year olds) have been widely used in South Africa since the 1970's although no studies have been published in peer reviewed journals. Luiz et al (1993) have reported in university publications several studies of the use of the scales in our diverse population. She has shown this assessment to be applicable for the South African population and comparable to the JSAIS.

Luiz and Heimes (1993) have shown a high correlation between the General Intelligence Quotient (GIQ) of the JSAIS and the General Quotient (GQ) of the Griffiths Scales. The scores on the Griffiths tend to be higher. Further in-depth assessment of the hearing and speech subscale by Luiz in the same publication indicates a high correlation between this and the Reynell Verbal Comprehension Scale A (Reynell, 1977) although the children did obtain higher mean age scores on the Reynell.

Allan et al (1992) compared the performance of white South African children to the British normative sample (1960) and found these norms not to be applicable. However, if more recent British norms (1980) were applied they were entirely applicable. Allen also translated the test into Afrikaans and Xhosa. In a further study in the same year Allen et al compared the four ethnic groups in South Africa on the scale and found no significant differences on GQ. There were, however, differences on individual scales. In conclusion he found the scores of white and Indian children to equate to the 1980 norms and those of black and coloured children to equate 1960 British norms. He suggests that national multi-cultural South African standards for the Griffiths Scales may not be possible.

Because of the cultural bias found in some of the items in the hearing and speech subscale culturally neutral items have recently (1997) been introduced and are recognised by the Association for Research in Infant and Child Development for use in our population.

3.4.4 Correction for gestational age

This remains an unresolved issue in the follow-up of the high-risk preterm infant. Miller et al in 1984 suggested that correction of DQ in preterm infants leads to an underestimate of disability in these infants and may hide those at risk for later learning problems. They felt that the uncorrected quotient more readily distinguishes abnormality and suggest that both corrected and

uncorrected scores should be evaluated. DiPietro and Allen in 1991 extensively discussed the issue of gestational ageing and its effect on developmental assessments. They indicate that the difference in corrected and uncorrected scores is greatest at lower gestational ages and small errors in age estimation lead to large differences in developmental quotients. This is less of a problem as the child gets older but if age correction is used at later ages it can increase the score by six points on average. It has been suggested by these authors that partial correction may be appropriate but that correction in infancy is probably applicable especially for parents when its use can reduce excessive parental concern without raising expectations. The recent opinion of Bowen et al in 1996 is that the developmental quotient in preterm infants should be corrected for gestational age at birth up to at least three years of age. His opinion is that using uncorrected scores leads to a gross overestimation of the number of children with intellectual disability. Other opinion indicates that correction to eighteen months or two years of age is appropriate but that there is some place for evaluation of both corrected and uncorrected scores (Barrera et al, 1987; Miller et al, 1984).

3.4.5 Evaluation of neurodevelopmental assessments

Recent studies have repeatedly emphasised the need for appraisal of predictive validity of neurodevelopmental assessments (Harris and Langkamp, 1994, Majnemer et al, 1998). This measure of a test is useful as it makes it clear to the clinician how predictive the evaluation is for abnormality or normality at a later date. It is especially useful in the newborn and early infant tests where the purpose of the assessment is to identify correctly the infants who are either abnormal or will be in need of further follow-up.

3.5 Conclusions

The incidence of high risk infants, both preterm and term, is much higher in Africa. Despite a decreasing incidence of birth asphyxia in the developed world, no such decrease is apparent in Africa, but a lack of comparable data precludes any real evaluation of the situation here. Much work needs to be done in Africa in order to document the current status and to monitor future trends.

Outcome in the developed world of the VLBW infant is generally good with survival intact of around 80%. The outlook for the smaller infants, especially the ELBW infants, is less favourable at about 50%. In Africa the proportion of VLBW survivors who are ELBW is small due to selective ventilation and the multiply disabled survivor in this weight category is seldom seen. The impact of the learning disabled VLBW survivor is being felt more keenly world wide and will surely have an even larger impact in Africa where the resources for specialised education are limited in the cities and non-existent elsewhere. Fetal growth restriction is a risk factor in all infants and with the increased incidence of growth restriction in some areas in Africa it is another additional factor in the already weighted scale of risk.

HIE is an area where much work remains to be done. In Africa we are still needing accurate data with regards to incidence of HIE and its outcome. Much work needs to be done in the area of prevention with good obstetric and labour practices as well as effective resuscitative techniques. In the rest of the world progress is required in the area of intervention to reduce cerebral damage. The outlook for the infant with severe HIE remains dismal wherever he is born.

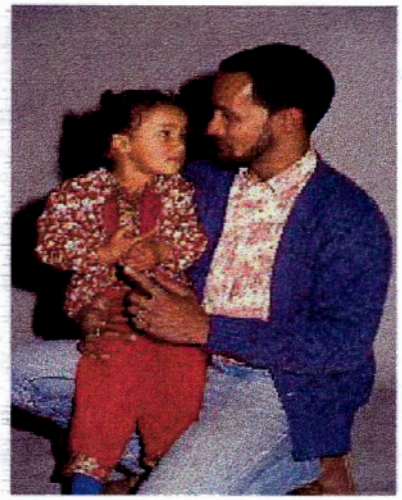
If it is not possible to lessen significantly the risk for newborn infants in Africa, it should at least be possible to identify those at risk early and intervene to lessen their long term disability. Early, effective, neurodevelopmental evaluation is possible and should be routine in the follow-up of these infants. Late follow-up for the borderline children should be possible too, so that the burden of learning disability in the already limited schooling system may perhaps be lessened.

The Griffiths Scales of Mental Development have been extensively tested in the South African population and are helpful in identifying the at-risk child and monitoring his progress.

This work is set out to evaluate the situation for the high-risk infant in Cape Town and to propose a protocol for the effective follow-up of these infants in Southern Africa.

Chapter 4

Follow-up of the VLBW infant



Tracy, birthweight 1000 grams, at follow-up

at age two years with her father.

4. Follow-up of the VLBW infant

4.1 Introduction

Groote Schuur Hospital (GSH) is one of two tertiary hospitals in the Cape Town Metropolitan area. It has a 60 bedded neonatal unit and 12 of these beds are intensive care beds with ventilation facilities. Together with Tygerberg Hospital and two secondary level hospitals in the near vicinity, GSH is the referral centre for VLBW infants born in the Peninsula and surrounding areas. Prior to this study, a comprehensive long term follow-up and audit of neonatal outcome, including mortality, had not been done from this unit. The study was planned following Marlow's publication in 1987 indicating 1250 g birthweight as an appropriate cut off weight for the highest risk infants.

4.2 Method

From July 1988 all live infants with a birthweight less than 1250 g born at, or referred to Groote Schuur Hospital's Neonatal Intensive Care Unit (NICU) over a 12 month period were prospectively included in the study cohort. After hospital discharge infants were seen at six weeks corrected age, 18 weeks corrected age and nine months of age and the Griffiths Scales of Mental Developmental (Griffiths, 1976) were applied at one, two and six years of age. At one year of age 106 infants were assessed, 96 at two years and 80 at six years. At six years of age the children were matched with 70 controls who had normal birthweights.

All the infants were cared for according to standard management practices in the NICU. Because of limited resources, infants under 900 g birthweight and 28 weeks gestation are not routinely ventilated. The decision to ventilate these smaller and younger infants depends largely on the availability of a ventilator and the maternal obstetric and social history. When a ventilator is available larger infants are ventilated when oxygen requirements exceed 80% and/or the infant has recurrent apnoea. Surfactant was not available or used at that time and the use of antenatal steroids was not routine.

Detailed information of antenatal and perinatal events as well as descriptive data for each infant were recorded. Each infant's gestational age was scored in the first week of life using the

Dubowitz method (Dubowitz et al, 1970). When an infant died before being scored, the antenatal ultrasound examination, the mother's expected date of delivery and clinical examination were used to estimate gestational age. Where clinically indicated, infants underwent cranial ultrasonography during the first week of life.

Survival and ventilation rates by 100 g birth weight subgroups and by gestational age were documented. Perinatal morbidity was documented for three weight categories: less than 900 g, 900 g to 999 g, and 1000 g to 1250 g.

Following the recommendations of Fawer and Calame (1988), surviving infants were followed - up until six years of age. At each visit a full clinical examination and neurodevelopmental evaluation (Magasiner et al, 1997) comprising an assessment of tone, postural responses and primitive reflexes were carried out. At one, two and six years of age the Griffiths' Scales of Mental Development were performed (Griffiths, 1976). Infants with cerebral palsy were referred for neurodevelopmental therapy (NDT) and those with squints for ophthalmological assessment. At nine months, a hearing screen was performed with the Manchester high frequency rattle (Van Zyl, 1984) and at two years, a formal hearing assessment was done using free field testing and impedance evaluation (Sheridan, 1968). At six years of age anthropometric data was also recorded for both index and control children.

In order to assess the social status of the cohort, a research assistant was employed to undertake home visits after each infant's hospital discharge. The home conditions and financial status of the family was evaluated. This contact with the family also enabled infants who defaulted from follow-up visits to be more easily traced.

Matching controls for the six year old children were selected from the community. A research assistant visited the index family and evaluated the suitability of available controls in the index household or nearest neighbouring household or, failing that, at the local pre-school or child care facility. Controls were matched for sex, age and socio-economic status. Their pre-school card was perused for birthweight >2500g, normal Apgar scores and uncomplicated perinatal course with early discharge home. If more than one control was available the child nearest in age to the index child was chosen.

Scoring of the Griffiths Scales of Mental Developmental was done for corrected and uncorrected age at one and two years and uncorrected age only at six years (Miller et al, 1984). A normal developmental quotient (DQ) was considered to be a score of 80 or more, borderline DQ 70 - 79 and abnormal DQ less than 70. Major disability at one and two years of age was considered to include infants with cerebral palsy (CP), infants with a DQ less than 80 and those who were blind or deaf. (CP is defined as a disorder of movement and posture due to a defect or lesion of the immature brain (Bax, 1964)). Minor disability was considered to include infants with developmental delay and a normal DQ, clinically assessed hyperactivity and squints. At six years of age children with DQ's between 70 and 80 who were likely to have later scholastic difficulties were included in the minor disability group together with those children assessed as having attention deficit and hyperactivity.

Statistical analysis of developmental quotient results using two sample analyses was undertaken in an attempt to identify specific 'high-risk' categories within the cohort. Individual Griffiths scale results were compared for sex (male versus female), place of birth (inborn versus outborn), maternal booking status (booked versus unbooked), gestational age above and below 28 weeks, and birth weight above and below 1000 g, as well as comparing the UGA and the appropriately grown infants. The effect of neonatal morbidity on outcome was also assessed by comparing those ventilated to those not ventilated, and by comparing infants with or without bronchopulmonary dysplasia (BPD), apnoea or necrotising enterocolitis (NEC). In order to assess further trends present in the cohort, multivariate cross correlation analysis as well as regression analysis for birth weight, gestational age, 5 minute Apgar score and duration of ventilation was performed.

4.3 Results

Social

The infants managed in this intensive care unit are largely from poor socio-economic backgrounds (Wescott et al, 1986). The family circumstances of 84% of the study infants were assessed by a research assistant and 76% of the survivors were visited at home. (The remaining 24% lived either out of Cape Town or could not be visited due to socio-political unrest in the

informal settlement areas at that time). Seventy six percent of the families assessed were poor and could be classified as social class V (Molteno et al, 1980). Only 46% of parents were married.

Survival

Two hundred and thirty five infants with a birthweight less than 1250 g were admitted to the GSH NICU in the 12 month period, most of whom were born at GSH. Ten percent were outborn, mainly in the Cape Metropolitan area, and transported to GSH by ambulance under the care of neonatally trained ambumedics. One hundred and forty three infants survived to hospital discharge. Figure 4.1 shows a breakdown of survivors and infants who died (including numbers ventilated) and indicates the distribution of early (less than 8 days), late (8 to 28 days) and post neonatal deaths (over 28 days).

Figure 4.1: Early outcome of the study infants

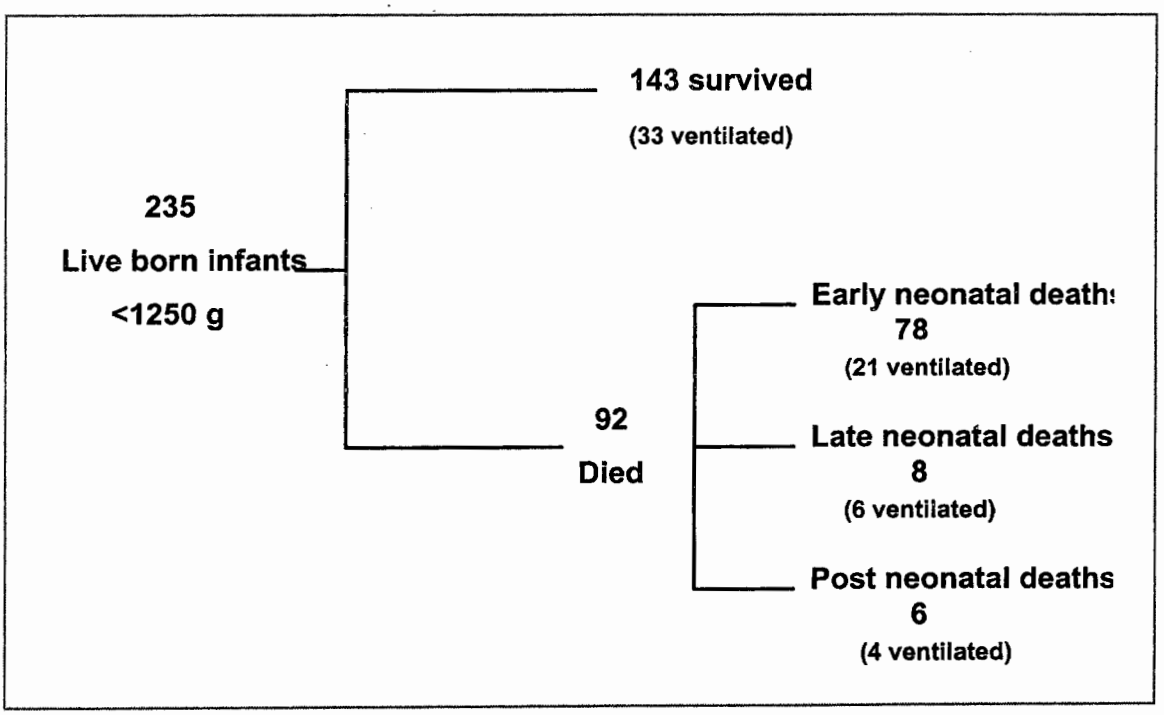


Table 4.I: Ventilation and survival rates by birthweight

Weight (g)	Number	Discharged alive	Ventilated	Survived ventilation
<800	50	10 (20%)	7 (14%)	3 (43%)
800-899	37	23 (62%)	10 (27%)	6 (60%)
900-999	39	20 (51%)	15 (38%)	4 (36%)
1000-1099	41	31 (76%)	14 (34%)	8 (57%)
1100-1199	48	40 (83%)	13 (27%)	7 (54%)
1200-1249	20	19 (95%)	5 (25%0	4 (80%)
Total	235	143 (61%)	64 (27%)	32 (14%)

Table 4.I and figure 4.2 categorises the infants within 100 g birth weight subgroups. Survival and ventilation rates are compared within these subgroups. Some infants were not ventilated because of clinically assessed extreme immaturity and this explains the low numbers of infants who were ventilated under 900 g.

The survival rate for the cohort was 61%. As expected, survival rates improved with increasing birth weight. The survival rate below 1000 g was 42% but it doubled to 83% for those infants with birthweights of 1000 g or more.

An analysis of the survival of infants within gestational age subgroups showed the survival rate under 30 weeks to be 34% and from 30 weeks to be 87% (Figure 4.3).

Figure 4.2 Outcome of the VLBW cohort by birthweight, showing numbers ventilated.

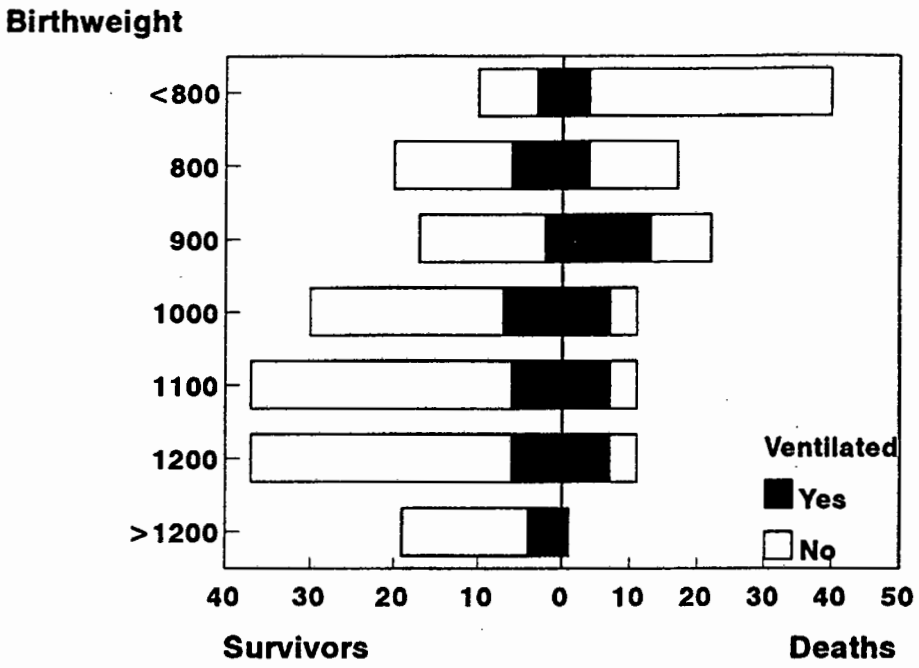
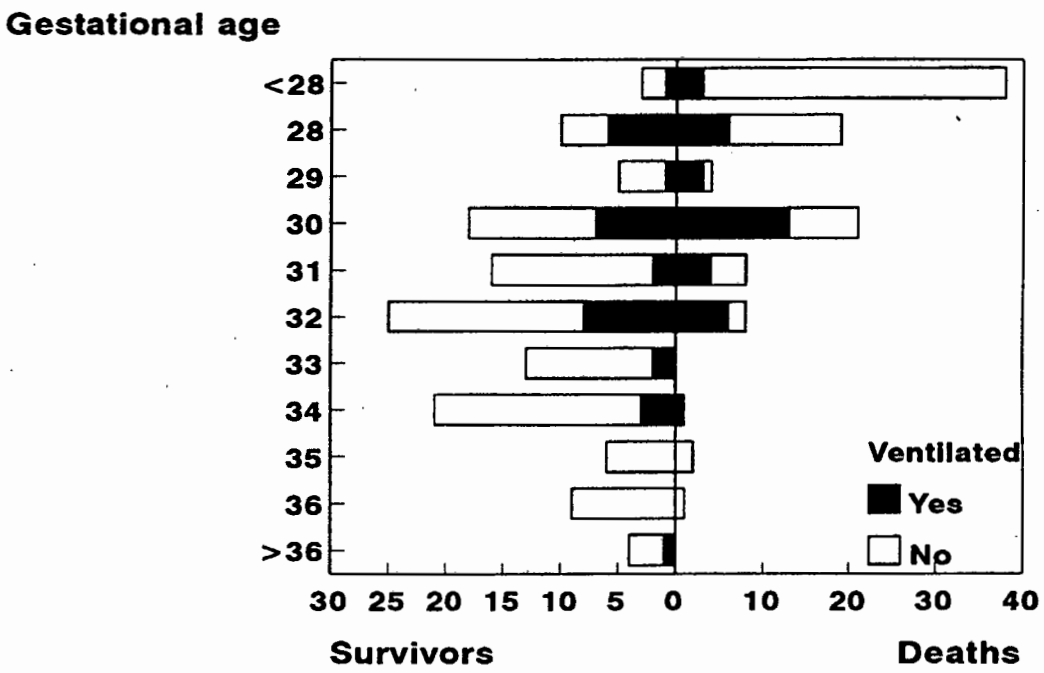


Figure 4.3 Outcome of the VLBW cohort by gestational age, showing numbers ventilated.



Perinatal data

Tables 4.II compares the characteristics of the infants and their mothers between survivors and non-survivors.

As expected the mean birthweight and gestational age of survivors was significantly greater than that of infants who died. Sixty-nine percent of survivors were UGA of which 82% had weight and head circumference below the 10th centile expected for gestational age suggesting prolonged fetal growth restriction (Woods et al, 1979). A previous study documented growth curves for the local population (Malan et al, 1967) and found them to be almost identical to those of Lubchenco in 1966. Overall the Lubchenco growth curves are lower than other intra-uterine growth charts and the tenth centile therefore closely approximates two standard deviations below the mean.

Table 4.II: Characteristics of the infants and their mothers

	Infants who survived	Infants who died	P value
Infants:			
Number	143	92	
Male:female	71 : 72	48 : 44	NS
Birthweight			
Mean (SD)	1044 g (149 g)	846 g (192 g)	< 0.0001
Range	600 - 1250 g	400 - 1245 g	
Gestational age			
Mean (SD)	32 weeks (2.5)	27.9 weeks (3)	< 0.0001
Range	(26.8 - 40) weeks	(21 - 36) weeks	
UGA	98 (69%)	22 (25%)	< 0.0001
Mothers:			
Age (mean years)	26	26	NS
Teenagers	20%	12%	NS
No antenatal care	20%	38%	0.003
GPH	35%	21%	0.03
Caesarean section	42%	24%	0.004
Vaginal breech	12%	21%	NS

Mothers overall were of a similar age but a smaller proportion in the group whose infants died were teenagers. The significantly higher incidence of gestational proteinuric hypertension (GPH) in the mothers of surviving infants reflects the fact that these mothers receive hospital care, usually as inpatients, and their infants are delivered often after a course of antenatal steroids by elective caesarean section. With such intensive antenatal care these infants are more likely to survive.

Table 4.III compares perinatal morbidity for all infants by three weight categories. Under 900 g 30% of infants were intubated and actively resuscitated at birth. Over 900 g this increases to 50%. As expected the incidence of hyaline membrane disease (HMD) was higher in the lower weight categories. Approximately one fifth of infants under 1000 g had apnoea. Eighteen percent of infants less than 900 g and 37% of those 900 to 1000 g were ventilated. The incidence of pneumothorax was low (3 - 5%) as was that of BPD(4-6%). Less than 10% of all infants had necrotising enterocolitis (NEC).

Seventy-six infants (53%) underwent cranial ultrasonography of whom 49 (64%) were normal. Leucomalacia was diagnosed in five infants (6%) and intraventricular haemorrhage more severe than grade II (Levene and De Cresigny, 1983) was shown in 11 infants (14%). Table 4.III shows IVH data for survivors only.

The incidence of congenital abnormalities was 9%; three infants with fetal alcohol syndrome (FAS), seven with inguinal hernia, two with hypospadias and one with undescended testes.

As expected the length of hospital stay decreased with increasing birthweight. The mean hospital stay for survivors was 58 days (range 20 - 135 days). The mean hospital stay for infants who died was 11 days (range 1 - 48 days).

Table 4.III: Perinatal data by birthweight categories (deaths included).

Birthweight	<900	900 - 999 g	1000 - 1249g
Number	76	46	113
Survived	27 (36%)	24 (52%)	92 (81%)
Died	49 (64%)	22 (48%)	21 (19%)
UGA	47%	54%	52%
Intubation at birth	23 (30%)	23 (50%)	37 (33%)
HMD	39 (51%)	28 (61%)	40 (35%)
Apnoea	18 (24%)	13 (28%)	18 (16%)
Ventilated	14 (18%)	17 (37%)	33 (29%)
Pneumothorax	2 (3%)	2 (4%)	6 (5%)
BPD	4 (5%)	3 (6%)	4 (4%)
Ventilation (mean days)	6	9	8
NEC	5 (7%)	2(4%)	7 (6%)
Stay (mean days)	40	37	30
IVH (survivors only)			
no of U/S done	15	15	37
Grade I & II	5	8	9
Grade III & IV	2	1	2
PVL	2	0	1

Outcome

Deaths (Figure 4.1)

Ninety-two infants died in hospital, 86 (37%) within the first 28 days. Eighty-five percent of deaths occurred within the first week of life and one quarter of these infants died soon after delivery (19 infants). The main causes of death prior to discharge from the unit were immaturity and HMD. Infants with birth weights less than 900 g accounted for 37% of the total births and 59% of the

mortality. Infants weighing 1000 g or more at birth accounted for 46% of births and 20% of deaths.

Eleven infants died in the first six months after hospital discharge. Three infants died from sudden infant death syndrome (SIDS), five infants from infection and three infants from unknown causes. Only one infant had a post mortem examination which confirmed the clinical diagnosis of SIDS. Except for this infant and one infant who died in hospital, all the causes of death were based on the history given by the mother.

No infants are known to have died after their first year except for one child who died in her sixth year from a cerebral tumour.

Follow-up

Figure 4.4: Follow-up to 6 years of age

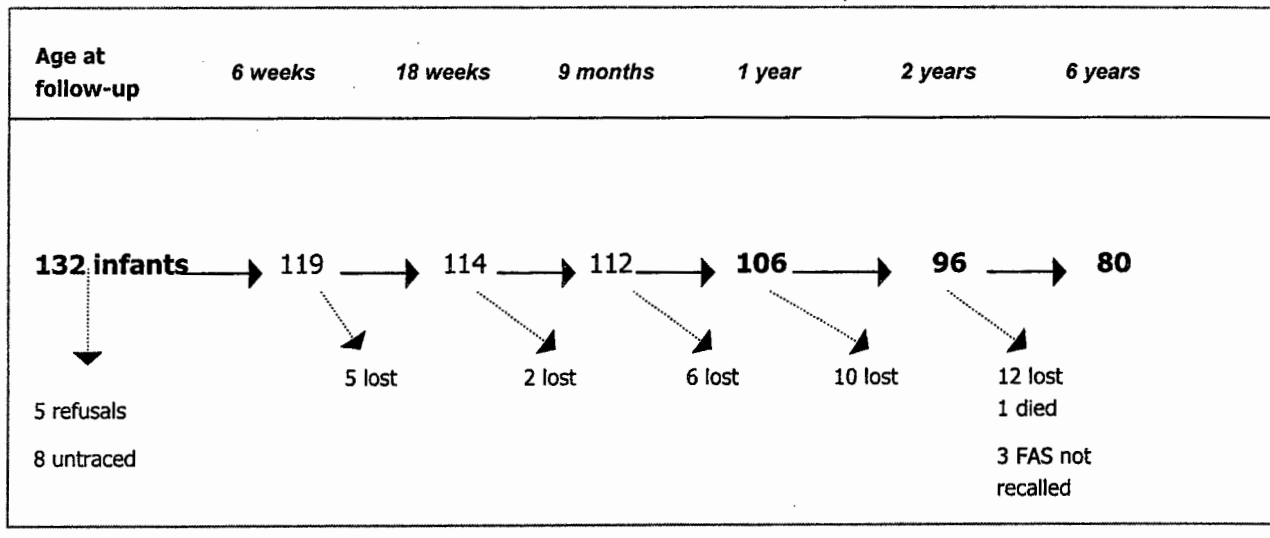


Figure 4.4 shows that of the 143 infants discharged alive, 132 formed the cohort for long-term follow-up (11 infants died after hospital discharge). One hundred and six infants were assessed at one year and 96 at two years. Eight infants were never traced after discharge from hospital. The parents of five infants refused to participate in the study. The remaining 13 infants were lost

some time in their first year as indicated. Of these, five were thought to be abnormal at the last visit. Ten infants who were normal at one year could not be traced at two years.

Eighty children in total were re-evaluated at six years of age. Between two and six years of age seven children had moved away from Cape Town, five were untraced, one had died and the three children with FAS were not recalled.

Outcome under one year (Figure 4.4)

The outcome of the eight infants never traced after hospital discharge is unknown. One of the five infants whose parents refused participation in the study had hydrocephalus requiring shunting in the perinatal period and was abnormal when examined prior to hospital discharge. Two of the five infants seen only at six weeks of age showed excessive truncal extension with some increase in lower limb tone. Of the two infants followed only until 18 weeks, one was found to have poor trunk control with excessive head lag. Two of the six followed only until nine months were abnormal; one with severe developmental delay and the other with generalised hypotonia.

Outcome at one and two years of age including Griffiths assessments

The mean developmental quotient of 106 Griffiths assessments at one year of age was 90 (SD 11; range 28-108) and of 96 Griffiths assessments at two years of age was 91 (SD 13; range 21 - 112). Table 4.IV shows the mean scores and standard deviations (SD) at one and two years of age (corrected and uncorrected) for the whole cohort and for the cohort excluding the infants with FAS and CP.

The mean scores were significantly less for all scales at two years compared with one year and this comparison can be seen in Table 4.V.

Table 4.IV: Griffiths scores at one and two years of age with and without FAS and CP infants

Cohort	Uncorrected scores at 1 year	Corrected scores at 1 year	Uncorrected scores at 2 years	Corrected scores at 2 years
Whole cohort	90 (11)	104 (13)	85 (12)	91 (13)
Cohort excluding FAS and CP infants	92 (7)	106 (8)	87 (7)	93 (8)

Table 4.V: Griffiths' Assessment Scale Results at one and two years (corrected scores; mean (SD))

Scale	1 Year	2 Years	P value
Locomotor	102 (16)	94 (15)	0.0003
Personal and social	105 (15)	94 (16)	<0.0001
Hearing and speech	109 (13)	88 (12)	<0.0001
Eye and hand	100 (15)	89 (14)	<0.0001
Performance	100 (16)	87 (15)	<0.0001
Practical reasoning		93 (16)	<0.0001

Disabilities at one and two years of age

Major disabilities (Table 4.VII)

At one year:

Six infants were diagnosed as having cerebral palsy (5,7%) at one year of age. Three of these infants manifested mild spastic hemiplegia with normal DQ's and three had severe spastic quadriplegia with DQ's less than 50. Using uncorrected DQ's, six infants, including two with FAS and one with developmental delay, were in the borderline range of DQ (70 - 79). None of the neurologically normal infants scored less than 70 nor were any of the 106 infants blind or deaf.

By 18 weeks corrected age five of the six cerebral palsied infants had been recognised as having deviant motor development and referred for NDT. The sixth infant attended follow-up at six weeks and was clinically normal but then defaulted from follow-up until one year of age when she presented with spastic quadriplegia.

At two years:

One infant who was assessed as normal at one year showed signs of a mild spastic diplegia with a normal DQ at two years of age. Another infant who had mild hemiplegia at one year showed no abnormal signs at two years. The number of infants with cerebral palsy by the second year therefore remained unchanged. The DQ's of the three infants with severe cerebral palsy remained less than 50. Using uncorrected Griffiths' scores at two years of age fourteen infants, including one with FAS, had a borderline DQ and were assessed as possibly intellectually disabled (ID) without evidence of cerebral palsy. Only one infant scored less than 70 and he had FAS. Three of six normal infants categorised as intellectually borderline at one year of age were normal at two years with DQ's more than 80. None of the neurologically normal infants had a DQ of less than 70. None of the infants examined at two years of age was blind. One infant in the intellectually borderline group was thought to have some conductive hearing impairment but she never attended a formal hearing assessment.

Minor disabilities

At one year:

Four infants required ophthalmological intervention for strabismus. Two of the four fell into the cerebral palsied group with spastic quadriplegia. One further infant had significant motor developmental delay with a DQ in the normal range but this infant was ill with tuberculosis when seen at one year of age.

At two years:

Three infants were clinically assessed as hyperactive and extremely distractible, without signs of CP or ID.

Outcome at six years of age including Griffiths assessments (Table 4.VI and figure 4.5)

Twelve children were lost between the second and sixth years and one died. Twelve of these 13 children were normal at their last assessment and one was in the borderline intellectual range (DQ 70 - 79) at two years of age. The children with FAS were not recalled at six years of age. Two of the three children with FAS were functioning in the borderline intellectual range and one had a mild ID at two years of age.

Because of the impact of environment on childhood intellectual development, it was necessary to assess the children at six years of age together with normal birthweight controls matched for age, sex and socio-economic status. 75 index children were seen with 70 controls. The index children with CP were seen separately without controls.

The mean DQ of 75 Griffiths' assessments on the VLBW children was 92 (SD 8; range 65-109). The mean DQ of 70 controls was 99 (SD 8; range 80-117) and was significantly greater ($p<0,005$). This significant difference in quotients between controls and index children occurred in all six scales as shown in the graph (Figure 4.3).

Figure 4.5: Comparison of Griffiths Scale results between index (I) and control (C) children at 6 years of age

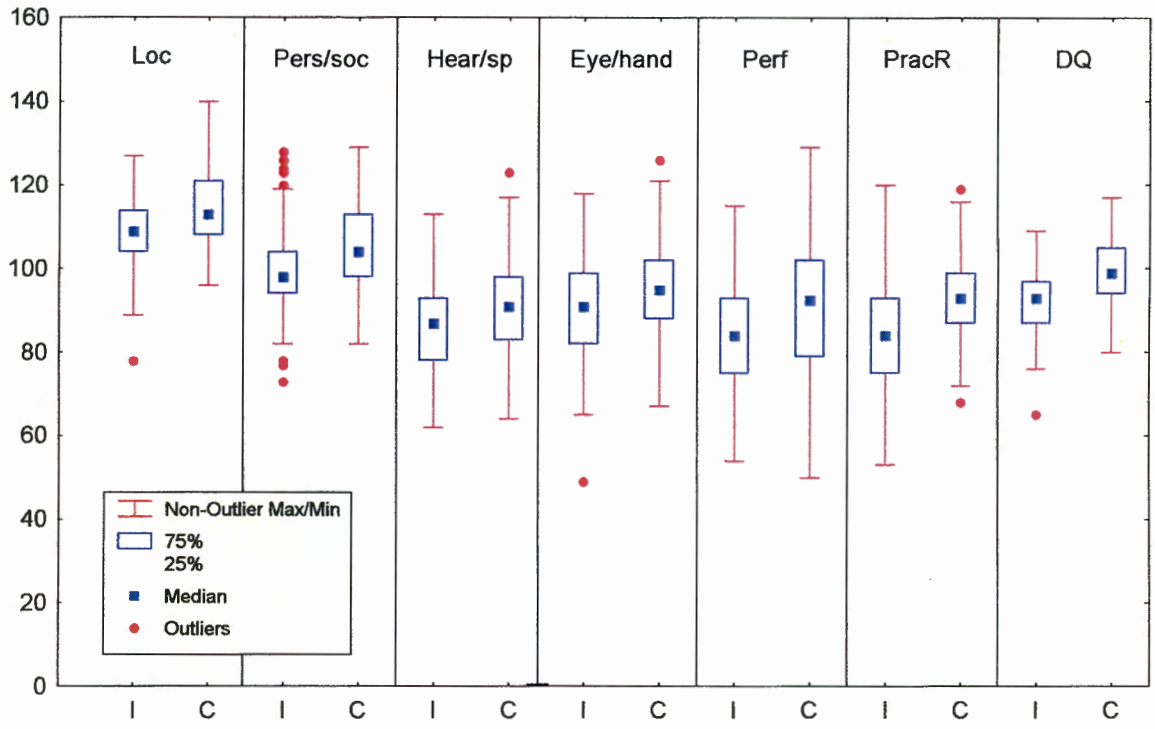


Table 4.VI: Griffiths results (mean and SD) for index and control children at six years of age

Griffiths Scale	Index children	Control children
Locomotor	108(10)	115(10)
Personal and social	99(11)	105(11)
Hearing and speech	85(18)	90(12)
Eye and hand	90(12)	95(12)
Performance	84(12)	92(16)
Practical reasoning	84(13)	93(11)
DQ	92(8)	99(8)

Disabilities at 6 years of age

Major disability(Table 4.VII)

At six years:

At six years of age, five of the six children with CP at two years still had signs of CP. Three of the five were severely disabled with DQ's <50 and two were hemiplegic with normal DQ's and were at school. One of the children showed no signs of the mild diplegia evident at two years of age and he was assessed with the rest of the cohort with a matched normal birthweight control.

One child's DQ was less than 70 and three others fell in the borderline range (70 - 79). Twenty index children scored in the low normal range (80 - 89). In total, four of 75 index children or 5% of the cohort were ID or had borderline intellectual function at age six. These four children all had normal uncorrected scores at age two, although all were in the low normal range (80 - 90). Of the 14 children identified as intellectually disabled using uncorrected scores at two years of age, four were normal, seven were low normal and three were lost to follow-up at six years of age.

Of the 70 control children assessed, none had a DQ less than 80, ten were in the low normal range (80 - 89) and the rest were in the normal range.

Minor disability

At six years:

Of the normal cohort seen at six years of age, 58 index children with 58 control children were assessed for attention deficit hyperactivity (ADH) using clinical observation and a maternal questionnaire (Coetzer, 1995). Ten of the index children (17%) were assessed as ADH and two (3,4%) of the controls.

Summary of outcome of the VLBW cohort over six years

The overall disability rate (major and minor disability) at one year was 14% with a major disability rate of 11%. The overall disability rate at two years was 25% with a major disability rate of 22%.

At six years of age this rate had decreased to 8% (major) and 16% (minor) disability or 24% total disability.

Table 4.VII summarises the outcome of the cohort over six years and table 4.VIII shows outcome at 6 years of age by birthweight category. Except for one of the children with CP, all the disabled children had birthweights more than 1000 g.

Table 4.VII: Neurodevelopmental outcome over a six year period of infants weighing less than 1250 g at birth

	1 year (n= 106)	2 years (n = 96)*	6 years (n = 80)**
Lost to follow-up	26[#]	10[+]	16
Normal	91	72	71
CP:			
Spastic quadriplegia	3	3	3
Hemiplegia	3	2	2
Spastic diplegia	0	1	0
DQ <70:			
With CP	3	3	3
Without CP	0	1	1
DQ 70-79:			
With CP	0	0	0
Without CP	6[$]	14[++]	3
ADH: (n = 58)	0	3	10
(normal DQ, no CP)			
Squint:	4	0	0
Developmental delay:	1	0	0

* Three FAS infants included

** Three FAS children excluded

[#] Six infants abnormal at last assessment

[+] All normal at last assessment

[$] Includes two infants with FAS

[++] Includes one infant with FAS

Table 4.VIII: Outcome at 6 years of age by birthweight category

	<900 g	900 - 999 g	1000 - 1250 g
Normal	12	13	46
CP:	1	0	4
DQ <70			
With CP	0	0	3
Without CP	0	0	1
DQ 70 - 79	0	0	3

The value of the Griffiths Developmental Assessment

The corrected DQ has been shown to underestimate disability in the preterm infant (Miller et al, 1984). For this reason we calculated both the corrected and uncorrected scores and used both to obtain a range of disability at one year and two years (Table 4.IX). The disability rates quoted thus far have been those obtained using the uncorrected DQ. Using the corrected DQ the major disability rate falls to 7% at one year (one borderline DQ, six CP (three with DQ<70)) and to 10% at two years (four borderline DQ, six CP (three with DQ<70)). The difference in numbers of infants detected with borderline intellectual ability becomes statistically significant only at two years of age.

At six years of age, where developmental assessment becomes more accurate and developmental quotients begin to more accurately reflect later intelligence quotients (Bowen et al, 1996), we found only one child in the ID range and three in the borderline range of intellectual function. None of these children were identified by either their corrected or uncorrected scores at 2 years of age. The use of uncorrected scores did tend to over estimate the amount of disability in the cohort.

Table 4.IX: Intellectual disability: Corrected versus uncorrected scores at one and two years of age (infants with CP and FAS included).

	DQ <80	Normal	P value
One year:			
Corrected score	4	102	
Uncorrected score	9	97	NS
Two years:			
Corrected score	7	89	
Uncorrected score	18	78	0.03

Griffiths developmental scores at one year correlated well with those at two years. Two sample analysis of perinatal variables did not demonstrate any significant differences in DQ, except infants with and without NEC (p = 0.007). Notably the comparison of extremely low birthweight to very low birthweight infants, and gestational age above and below 28 weeks, showed no significant differences in DQ results. Outborn infants scored as well as those born at GSH. At two years of age there was a tendency for the UGA infants to score less well (p = 0,053). This trend was not apparent at one year nor at six years but the numbers in the final six year old cohort were small. The duration of ventilation did not have a statistically significant effect on Griffiths score.

There was a significantly negative correlation (p = 0,02) between gestational age and the Griffiths DQ. The DQ tended to be lower in the higher gestational age groups. The infants at or near term were extremely growth restricted and likely, as other studies have shown (Greison et al, 1989), to score less well.

An assessment of the effect of social status on outcome revealed that infants from higher income groups scored significantly higher (p = 0,014) in the Griffiths assessment. This has been a

universal finding in many follow-up studies (Ornstein et al, 1991). Marital status of the parents had no effect on the DQ.

Anthropometric data at six years of age

At six years of age the heights, weights and head circumferences of 66 index and 59 controls were measured. All three measures were greater in the control children reaching statistical significance for weight and head circumference. Table 4.X shows the mean measures for both the index and control children.

Table 4.X: Mean height, weight and head circumference measurements for the VLBW and control children at six years of age.

Measurement	Index children	Control children	P value
Weight	17,6	19	<0.001
Height	112	113,5	0.12
Head circumference	50	51	<0.01

4.4 Discussion

It is important for every neonatal unit to assess the outcome of its graduates and, in the light of data obtained, alter or confirm its own management protocols. The NICU at GSH offers the unique opportunity to study neonatal outcome from a facility serving a developing community. Comparison of data with those from other neonatal intensive care units must be made with caution, bearing in mind the differences in population, management protocols and available resources. An ongoing collaborative study by Hack et al (1991) clearly demonstrates important and major inter-centre variations of neonatal outcomes even when data are collected with a uniform protocol. Despite these differences it is useful to compare the data presented here with some international standard.

The survival rates at GSH NICU are comparable with those of Hack et al (1991) and other studies (Kitchen et al, 1991; Grogaard et al, 1990) and are almost identical to a local study by Van Der

Griendt et al(1992). The high percentage of UGA infants (Table 4.III) reflects the low income group served by this unit, the high incidence of gestational proteinuric hypertension, and the characteristic feature of mothers in the Cape Province who tend to be thin, short and underweight (Woods et al, 1978) and produce UGA infants (Woods et al, 1979).

In the surviving infants the incidence of congenital abnormalities was equivalent to that of Elliman et al (1986). However, the incidence of FAS was notable in our cohort - again largely a reflection of the community served by the NICU at GSH. The sub-clinical effect of fetal alcohol is unknown but may also be an influencing factor in the percentage of underweight infants in this cohort.

A high percentage of mothers whose infants died received no antenatal care. This is a source of concern as antenatal care may improve the perinatal mortality rate from this unit.

When comparing results in this report with those of Hack et al (1991) sociodemographic and birth data are similar, including maternal age, race, marital status and percentage of mothers without antenatal care. There are, however, many areas in the perinatal data where marked disparities exist. At GSH the caesarean section rate is lower and vaginal breech delivery rate much higher. This implies less active interventional obstetric care and is directly related to our conservative policy for the extremely immature infant. It follows, therefore, that the incidence of endotracheal intubation at resuscitation is lower, especially in the infants weighing less than 900 g. The incidence of apnoea, HMD and percentage of infants ventilated is also considerably lower despite the fact that the GSH cohort was selected from infants weighing less than 1250 g. This is due to the tendency of infants in this cohort to be UGA and, therefore, on average more mature than those of Hack et al (1991).

The present study therefore differs from most others in that:

1. A large proportion of the surviving infants were UGA.
2. Relatively few infants with birth weights less than 900 g survived, due to conservative management policies.
3. The majority of families were of low socio-economic status

Do these factors influence outcome? It appears that the incidence of neurodevelopmental disabilities is not affected but the type of disability differs from other reports. Hagberg et al (1989) report the survival of increasing numbers of severely multiply disabled very preterm infants. Marlow et al(1987) clearly demonstrate an increasing disability rate under 1250 g and report that one fifth of the disabled infants had three or more major disabilities, especially visual and hearing impairments. None of the infants with major disability in this study had more than two disabilities and none were blind or deaf. This is likely to be related to decreased survival of the ELBW infant at GSH.

The major disability rate increased from 11% at one year to 22% at two years due to the detection of intellectual disability which is difficult to assess under two years of age (Teplin et al,1991). Evidence suggests that much abnormality may lie hidden in those infants who do not return for follow-up (Tyson et al, 1988, Wariyar and Richmond, 1989). If one assumes that all the infants in this cohort never seen after discharge from hospital (n = 8), and all those who showed abnormal signs when last examined (n = 7), were abnormal the major disability rate at one year is 20% and at two years is 30%. We feel that this is likely to be an overestimation of the actual situation and in fact the true disability rate is more likely to lie somewhere between the figures quoted. Literature reports similar major disability rates but most reports in the 1990's concern the ELBW infant (Kitchen et al, 1991;Saigal et al 1991; Veen et al, 1991; Collin et al, 1991; Doyle et al,1991).

The percentage of UGA infants was exceptionally high. Even excluding infants over 32 weeks gestation, 60% of the cohort was UGA. This is double that seen in other studies (Hack et al,1991;Elliman et al,1986). We acknowledge that recent studies have shown that scoring based on the Dubowitz method does overestimate gestational age in the VLBW infant (Sanders et al, 1991). It is documented that growth restricted infants generally do less well at pre-school testing (Ounsted et al, 1989; Goldenberg et al, 1998).

By 18 weeks corrected age we had detected a number of infants with abnormal signs on clinical neurodevelopmental assessment. All except one of the cerebral palsied infants were within this group. (The sixth CP infant defaulted until one year of age.) Griffiths Developmental Quotient assessment at one year of age did not detect more disability than already revealed by clinical assessment if the corrected score was used.

At two years of age only three neurologically normal infants had a corrected DQ less than 80. We also measured the uncorrected DQ at ages of one and two years. There is no consensus about correction of the DQ in preterm infants (Blasco 1989; Di Pietro and Allen, 1991). Some suggest correction always (Klein et al, 1989), others only up to one year of age (Siegel 1983), and still others say the DQ should never be corrected if one is reporting incidences of abnormalities (Miller et al, 1984). An attempt was made to resolve this issue with this cohort by reviewing our scores at two years of age and comparing to the outcome at six years of age. It is difficult to come to any firm conclusion in this controversial area. The infants identified at two years of age in the borderline range of DQ by either corrected or uncorrected score did not include any of the children in the borderline range at six years of age. Fourteen children were identified as borderline at two years of age by uncorrected score. At six years of age four of the fourteen were not seen (one refused, one moved away from Cape Town, one was untraced and the other child had FAS and was not recalled) and the other ten had DQ's in the normal range. The uncorrected score at two years of age tended to overestimate the number of borderline children and perhaps indicates that correction of score until age two is appropriate.

The other point to be discussed is whether the Griffiths developmental assessment is appropriate for developing communities, including those in South Africa. The mean DQ in all scales fell from one to two years but that for speech fell more than 20 points. This raises the question of the validity of the verbal sub-test, but could also be the result of the compounding effects of VLBW and social disadvantage. Mc Call's(1979) concept of a strong canalisation of development in early infancy, giving way to a greater influence of other factors, particularly environmental, from 18 to 24 months, may explain this fall off in DQ by two years of age. This is largely confirmed at six years of age. The verbal sub-tests of both index and control children were low, although the controls less so, and this is more likely to be explained by social class influences (Table 4.VI).

This study has failed to show any clear perinatal predictors of poor outcome. Many studies have concluded similarly (Ornstein et al, 1991). In our cohort the UGA infant scored less well at two years and, in fact, all except one of the infants with major disability at two years of age were UGA at birth. At six years of age we did not show any difference in DQ results when comparing UGA and appropriately grown children within the VLBW cohort but numbers were small. The infants with NEC in our study did poorly but this result may be weighted by two individuals with severe

NEC and perforation. These infants suffered many other perinatal problems and both had abnormal cerebral ultrasound examinations showing hydrocephalus and leucomalacia. They have major disability (both spastic quadriplegic with ID). Conclusions about the influence of NEC on outcome cannot be drawn as the numbers in this cohort were too small.

Studies that have shown correlation's with oxygen use and duration of ventilation concern the ELBW infant (Kitchen et al, 1991; Doyle et al, 1991) and in fact Kitchen et al showed their greatest decrease in neurological abnormality over time in the less than 800 g group. It is in this weight category that infants are most frequently not ventilated at GSH.

No difference in outcome was demonstrated either in the infants with birth weights above or below 1000 g (confirming previous local studies (Deeny et al, 1987)), or in those requiring or not requiring ventilation or in those with or without apnoea in the perinatal period. This finding is again likely to reflect the smaller numbers of infants born at GSH weighing less than 900 g who survive.

The mortality and morbidity data of this cohort are similar to those of other studies (Wescott et al, 1986; Elliman et al, 1986) although the post discharge mortality is higher than Eliman et al. This is likely to be a reflection of the socio-economic status of the community.

At six years of age the VLBW children were smaller, lighter and had smaller head circumferences than their normal birthweight controls. This finding has been universal in similar studies (Ornstein et al, 1991). The VLBW children also scored significantly less than their normal birthweight controls. This has been repeatedly shown in many studies (Aylward et al, 1989) from developed countries. This trend was apparent in all scales.

More in depth assessment of this cohort assessing motor function and visuo-motor perception has been published locally (Coetzer, 1995) and indicates that up to 60% of the VLBW children and 21% of the controls are likely to have learning problems at school. This finding may have implications for the education system in this country where schools are struggling to cope with normal children and where pressure of numbers in the classroom will make learning for these disabled children extremely difficult.

4.5 Conclusions

This study has described the characteristics of the VLBW infant at Groote Schuur Hospital. Most were UGA. Twenty-seven percent of infants with birth weights less than 1250 g were ventilated of whom half survived ventilation and 61% survived overall. Eighty-five percent of deaths occurred within the first week of life. Mothers who received antenatal care were more likely to have a live infant and in the study population gestational proteinuric hypertension had a protective effect on outcome probably because it necessitated hospital care. Attendance for antenatal care, a birth weight above 900 g and gestational age above 30 weeks were important factors in predicting survival of the very low birth weight infant at Groote Schuur Hospital neonatal intensive care unit.

Follow - up of the VLBW infant is more meaningful up to six years of age and indeed more revealing of true adverse outcome. This study has shown that at Groote Schuur Hospital, for infants with birthweights less than 1250 g, approximately eight percent of survivors were disabled and most of these disabled infants had cerebral palsy. Use of the corrected score seems appropriate to two years of age and is probably unnecessary after this age. Assessment at school going age allows a more accurate evaluation of abilities and also enables the clinician to detect those children who fall in the low normal and borderline range and who will be the individuals likely to struggle to learn at school. Five percent of children seen at six years of age had a DQ in the borderline range but many more had wide discrepancies in their scores between separate scales and this would indicate the likelihood of learning disabilities (Shapiro and Gallico, 1993). The implications for the present school system to adequately educate these children are large and these findings need to be taken into account with future educational planning.

Chapter 5.

Follow-up of the infant with hypoxic ischaemic encephalopathy and evaluation of the HIE Score

5. Follow-up of the infant with hypoxic ischaemic encephalopathy and evaluation of the HIE Score

5.1 Introduction

Perinatal asphyxia remains a major cause of mortality and neurodevelopmental disability in term infants. In developing countries the incidence of post asphyxial neurological damage is particularly high (Ariede and Weerasinghe, 1995; Molteno and Lachman, 1996). The clinical neurological sequelae in the immediate neonatal period following perinatal asphyxia are referred to as hypoxic ischaemic encephalopathy (HIE). These sequelae have been shown to be better predictors of outcome than Apgar scores and blood gases (Levene et al, 1986).

Hypoxic ischaemic encephalopathy was originally described by Amiel - Tison in 1969 and there have been numerous studies since then. Recently new technologies have become available to determine cerebral damage more accurately and earlier in the perinatal course. These technologies include computerised tomography scanning, magnetic resonance imaging, cerebral function monitoring, cranial ultrasound and doppler ultrasound of the middle cerebral artery (Gray et al, 1993; Hellstrom-Westas et al, 1995; Yokochi et al, 1996; Levene et al, 1989). These modalities are however not available in many neonatal units, and certainly not in developing countries. There is a need for a simple but reliable clinical method of predicting outcome.

The most widely used classification of HIE is that of Sarnat and Sarnat (1976) which groups affected infants into one of three categories -- mild, moderate and severe. The decision as to whether an infant falls into the moderate or severe category is at times difficult and the outcome of infants in the moderate group is variable. Application of this grading system is also time consuming and requires some paediatric expertise as well as access to electroencephalgraphy (EEG).

More recently three published studies have developed scores for HIE. Portman et al (1990) developed a score that predicts early morbidity and mortality. Two other papers developed scores

which have been related to long-term outcome. Lipper et al (1986) used the post asphyxia score and Bao et al the neonatal behavioural neurological assessment (1993). These latter scores are long - involving 17 or more measures and require some training. Both, however, have found value in the use of such scores to predict neurodevelopmental outcome.

A scoring system has been developed at Groote Schuur Hospital's Neonatal Intensive Care Unit which is numeric with fewer items. It is based on that of Sarnat and Sarnat but is much simpler and hopefully will fill the need in the developing world for an unsophisticated, yet predictive assessment of the infant with HIE. This chapter reports on the evaluation of this scoring system in terms of its predictive value for neurodevelopmental outcome at one and three years of age.

5.2 Method

Term infants of 37 weeks gestation or more (as determined by the Ballard Score (1979)) with clinical signs of HIE were selected for the study.

Forty-five infants, who were born at Mowbray Maternity Hospital or Groote Schuur Hospital or transferred there after birth from a referring Midwife Obstetric Unit, developed hypoxic ischaemic encephalopathy after birth were studied prospectively. Forty of the 45 infants were evaluated at or before 12 months of age by full neurological examination and the Griffiths Scales of Mental Development were applied to 35 survivors at one year of age. Twenty five children were traced and evaluated similarly at three years of age with matched controls. These controls were selected by a research assistant who contacted the index households and assessed the availability and suitability of children within the index household or in the nearest neighbouring household. The pre-school card was evaluated for birthweight >2500 g, and an uncomplicated perinatal course without any evidence of asphyxia (as assessed by Apgar score and time to hospital discharge with normal feeding patterns).

While in the NICU study infants were scored daily according to the HIE score (Table 5.I) by attending intensive care physicians until the score was zero or until hospital discharge.

The only objective investigation generally available in these Neonatal Intensive Care Units was cranial ultrasound. At least one cranial ultrasound examination was carried out, usually prior to hospital discharge. Infants were followed-up at 18 weeks and one and three years of age.

At 18 weeks of age an Infant Neuromotor Assessment was done (Magasiner et al, 1997) and at 12 and 36 months of age the Griffiths Scales of Mental Development (Griffiths, 1976) and a full neurological examination was performed by a paediatrician blinded to the infant's history.

Outcome was considered abnormal if there was clinical evidence of cerebral palsy or intellectual disability, defined as a Griffiths' general quotient less than 70.

The HIE Score

The score consists of a clinical assessment of nine signs (Table 5.I).

Tone. Progressing from normal or slightly increased peripheral tone in the mildly affected infant to the more severely affected infant who is generally hypotonic or completely flaccid.

Loc (level of consciousness). The assessment of level of consciousness is as described originally by Sarnat and Sarnat (1976). The mildly affected infant has a normal level of consciousness or is hyper alert and staring with normal or decreased spontaneous movement and exaggerated responses to minimal stimuli. The more severely affected infant progresses through lethargy to complete unresponsiveness ("stuporose" as described by Sarnat and Sarnat, 1976).

Fits (clinically apparent seizures). The score increases with increasing frequency of seizures.

Posture. This is assessed again as described by Sarnat and Sarnat (1976) but in this study an intermediate score of one is given to the infant who has mild to moderate HIE and who shows intermittent bicycling movements of the limbs together with fisting (thumbs flexed, adducted and opposed across the palms).

Moro, Grasp, Suck (The primitive reflexes: moro reflex, palmar grasp and suck reflex). These reflexes are normal in the mildly affected infant, poor or partial in moderate HIE and absent in severe HIE.

Table 5.I: The Hypoxic Ischaemic Encephalopathy Score

Sign	SCORE 0	1	2	3	Day / Date	1	2	3
Tone	normal	hyper	hypo	flaccid				
Loc	normal	hyper alert, stare	lethargic	comatose				
Fits	None	infreq <3/day	frequent> 2/day					
Posture	normal	fisting cycling	strong distal flexion	decerebrate				
Moro	normal	partial	absent					
Grasp	normal	poor	absent					
Suck	normal	poor	absent ± bites					
Resp	normal	hyper vent	brief apnoea	IPPV (apnoea)				
Font'l	normal	full not tense	tense					
Total score per day								

Resp (respiratory pattern). In mild HIE the infant breathes normally or hyperventilates. More severely affected infants have episodes of apnoea and may require ventilation.

Font'l (fontanelle tension). The more severely affected infant may have a full or tense (bulging) fontanelle.

Each sign is scored from zero to three and the score for each day is totalled. The higher the score the more severely affected the infant. The maximum possible score on any one day is 22. The score is equally applicable in a ventilated infant. It can not be applied in a paralysed infant.

The inter-observer reliability of the score was tested prior to the start of the study. Ten infants were subjected to scoring independently by two observers over a period of four days, yielding 40 paired scores. An inter-observer reliability coefficient of 0,87 was obtained.

5.3 Results

Forty-five infants entered into the study over a 10 month period. Five infants were lost to follow-up by one year of age. The outcome of 40 (89%) infants is known. Four infants, all of whom had been diagnosed with cerebral palsy, died before the one year assessment. Twenty five of the 36 children who were assessed at one year of age were seen again at three years of age. Two more children of the original cohort had died between one and three years of age and nine further children were lost to follow-up (five had moved away from the area, three were untraceable and one refused further assessment). Results quoted refer to the cohort of 40 infants in the first year and 25 infants at three years.

Mothers' profile: (Table 5.II)

Fifty-three percent of the mothers were primigravidae and 29% were teenagers. Sixty-three percent delivered vaginally, 18% with instrumentation and 15% by caesarean section (C/S).

Table 5.II : Characteristics of the mothers and their infants

	Number N = 40	%
Mothers:		
Mean age, years (SD)	24 (6)	
Black race	32	80
Primiparity	23	53
Teenagers	13	29
NVD	25	63
C/S	6	15
Instrument	7	18
Infants:		
Birthweight, g (SD)	3375 (502)	
range	2400 - 4950	
Male sex	27	68
I min APGAR <6	33	83
5 min APGAR <6	20	50
Mean cord pH (SD)	7,11 (0,12)	
Mean cord BD (SD)	14,21 (5,02)	
Seizures	33	83
Ultrasound:		
Normal	17	43
Oedema	11	28
SCL	9	23
HIE Score:		
Max peak score <11	14	35
Max peak score >15	13	33
Normal day 7	13	32

Infants' profile: (Table 5.II)

Two thirds of the infants were male. Fifty-eight percent were delivered at a tertiary hospital. Thirty-three (83%) had a one minute Apgar score less than six and the same proportion had seizures. Only one third of all the infants became neurologically normal by day seven (i.e. scored zero).

Thirty-eight infants had a cranial ultrasound. Another two infants had mild HIE and were discharged early before cranial ultrasound could be performed. Twenty-one infants (56%) had an abnormal cranial ultrasound. Of these abnormal scans, nine showed subcortical leucomalacia. One infant had a small intraventricular haemorrhage (not shown in table 5.II) and 11 showed cerebral oedema.

Thirteen (33%) infants had maximum HIE scores of more than 15, 14 (35%) 10 or less and the remainder (13 or 33%) between 11 and 15. The cohort was, therefore, evenly spread over the range of the score.

Outcome at one year:

Twenty three infants were normal (58%), 16 (40%) had cerebral palsy (CP) with varying degrees of developmental retardation and one infant was developmentally delayed (hypotonic with motor delay but functioning normally in all other areas).

Four of the 16 infants with CP had died in hospital before six months of age.

A Griffiths Developmental Assessment was performed on 35 infants at one year of age (the other infant was hospitalised with CP and uncontrolled seizures at the time of assessment). The overall mean general quotient was 92 (range 7 - 128). The neurologically abnormal infants had a mean DQ of 47 (range 7 - 101) and the normal infants 116 (range 94 - 128). There was a significant negative correlation between the DQ and the peak HIE score with a correlation coefficient of 0,7.

Figure 5.1: Infants with normal and abnormal outcome at one year of age: Mean daily HIE score with confidence intervals.

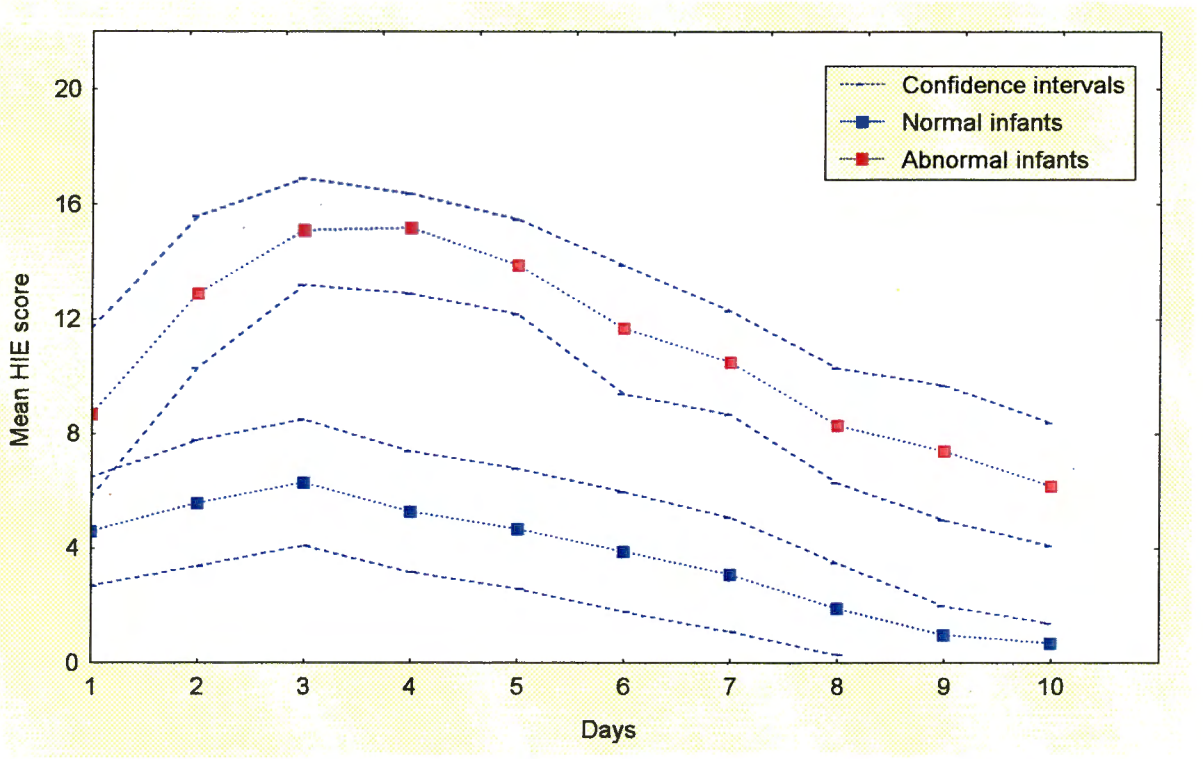


Fig 5.1 represents the mean daily scores and 95% confidence intervals of the normal (those infants who were normal at the one year assessment) and abnormal infants (those infants who had cerebral palsy at the one year assessment) over the first 10 days of life. There was a significant difference in mean HIE score throughout ($p = 0.03$ on day one and <0.01 thereafter).

Predictive values:

Predictive values for abnormal outcome for both for the score itself and for clinical findings associated with HIE were calculated (Table 5.III)

Table 5.III : Predictive values, sensitivity and specificity of the HIE Score for abnormal outcome at 1 year of age.

	PPV (%)	NPV (%)	Sensitivity (%)	Specificity (%)
Seizures	57	92	94	48
Leucomalacia	100	74	53	100
Max score >10	65	100	100	61
Score day 3 >10	73	94	94	74
Score day 4 >10	75	90	88	78
Max score>15	92	82	71	96
Score day 3 >15	89	71	47	96
Score day 4 >15	90	73	53	96
Abn score day 7	63	100	100	57
Abn day 7 and max score>15	92	100	100	93

The presence of clinical seizures had a positive predictive value (PPV) of 57% for abnormal outcome but a negative predictive value (NPV) of 92%. An infant with HIE who did not have seizures had a 92% chance of being normal. However, the presence of subcortical leucomalacia (SCL) had a PPV for abnormal outcome of 100%. All the infants seen at one year who had SCL on ultrasonography had CP (seven spastic quadriplegics and two microcephalic with hypotonic CP). The NPV was 74% ; some infants without SCL were abnormal.

Analysis of the HIE score also revealed some useful trends. All infants whose peak HIE score was 10 or less were normal at one year of age (i.e. the NPV of a maximum score greater than 10 was 100%). Sixty-five percent of infants with a peak score above 10 were abnormal whereas 92% with a peak above 15 were abnormal. Seventy percent of infants with a day three or day four score of more than 10 were abnormal (PPV 73% and 75% respectively) whereas 90% of infants with a score of more than 15 on these days were abnormal.

All those infants whose score had returned to zero by day seven were normal (the NPV was 100% for an abnormal score on day seven). When assessed in combination an infant with a peak score above 15 and who remained abnormal after day seven had a 92% chance of being abnormal. All infants who peaked below 16 and who were normal by day seven were normal (NPV 100%).

The infants were retrospectively classified into Sarnat and Sarnat categories by folder perusal by clinicians blinded to the outcome of the infants. The oculovestibular and tonic neck reflexes as well as the autonomic function parameters and EEG assessment were excluded. The results are shown in Table 5.IV

Table 5.IV: Number of infants with cerebral palsy related to Sarnat grading and maximum HIE score.

Number with CP/total in HIE score group	Maximum HIE score	Sarnat Mild	Sarnat Moderate	Sarnat Severe
0/10	0 - 10	0/10	0/0	0/0
3/13	11 - 14	0/0	2/12	1/1
14/17	15 - 22	0/0	2/2	12/15
Number with CP/total in Sarnat group		0/10	4/14	13/16

In this table the numerator of all fractions indicates the number of abnormal infants and the denominator indicates the total number of infants in the group. The majority of damaged infants were in the severe group. All infants in the mild group were normal. There were three CP infants in the moderate group and the infant with developmental delay also fell into this category. In general infants in the mild group had an HIE peak score of 10 or less, the moderate group 11 - 14 and the severe group more than 14. There were three infants whose HIE score fell out of these ranges. One infant in the severe group peaked at 14 and two infants in the moderate group peaked at 17.

Outcome at three years: (Table 5.V and Table 5.VI)

At three years of age the index children who were previously assessed as normal were evaluated with controls matched for age, sex and socio-economic status. In total 15 index children who were normal at one year were seen with 10 controls. The mean Griffiths DQ for the index children was 92 (range: 78-110) and for the control children was 95 (range: 80-105). This was not a statistically significant difference in DQ results, although the index children tended to score less on almost every sub-scale. The severity of HIE had no bearing on the DQ in the normal index children.

Of the nine children lost to follow-up all except one were normal at the one year assessment; the infant not seen for re-evaluation was motor delayed at one year. A further two children with CP had died between their first and third years. The remaining children with CP were reassessed: The 10 children remained abnormal, nine had CP with intellectual disability and one was mentally disabled without any evidence of CP. Of all the abnormal children only one was assessed as educable with a DQ >50.

Table 5. V: Griffiths Scores (means) at three years of age: Normal HIE survivors and their matched controls

Griffiths Scale	Index children (N = 15)	Control children (N = 10)
Locomotor	106 (15)	111 (14)
Personal/social	99 (16)	101 (15)
Hearing and speech	88 (13)	82 (7)
Eye and hand	85 (11)	90 (5)
Performance	84 (16)	92 (17)
Practical reasoning	92 (12)	93 (11)
Developmental quotient (DQ)	92 (10)	95 (8)

Table 5.VI: Outcome of the HIE cohort at three years of age

	One year (n = 45)	Three years (n = 25)
Lost to follow-up	5	9 (8 normal at one year)
Died	4 (all CP)	6 (all CP)
Normal	23	15
CP: DQ > 69	0	0
CP: DQ < 70	12	9
Developmental delay	1	0
DQ < 70, no CP	0	1

5.4 Discussion

It is evident from recent research that HIE in the long term produces a spectrum of neurological disabilities and impairments (Shaywitz et al, 1993; Robertson et al, 1993). Newer sophisticated diagnostic modalities will become more accurate in predicting these disabilities as research progresses, but these technologies are unlikely to become available in the developing world. What is needed in this setting is a simple clinical tool which will reliably predict the infant's outcome so that families can be provided with information as early as possible and plans for intervention for the disabled child can be implemented.

Two other studies have used a clinical grading system. The post-asphyxia score (PAS) of Lipper et al (1986) has 17 items and the neonatal behavioural neurological assessment of Bao et al (1993) has 20 items. In the latter paper the authors state that a two week training course is required before the clinician can use the assessment. It is not clear whether specific training for the PAS was instituted. Both methods appear to adequately predict neurological outcome early on in the perinatal course; that of Lipper et al was predictive even as early as 24 hours.

Robertson and Finer (1993) have found that the prognostic value of the stage of encephalopathy is greatest when the newborn neurologic examination is graded according to the most severe signs and evaluated over a seven day period. It is proposed that the grading system in this study, which incorporates some items from both previously published scores and which takes into account both the most severe signs and the length of persistence of these signs, is as accurate. It is also quicker to administer, requires no additional training for medical and paramedical personnel and requires no equipment. It is ideal for implementation at any district or rural facility where special investigations and specialist paediatricians are unavailable. It contains many of the features included in the three stages of Sarnat and Sarnat but excludes autonomic function, the deep reflexes and some of the primitive reflexes. We have added the grasp reflex, the respiratory pattern and a clinical assessment of the fontanelle tension since cranial ultrasonography is not generally available in developing countries.

Cranial ultrasonography data was reported as this was the only easily available investigation. These data are incomplete in that two of the 40 infants were not scanned. Both infants, however, were normal at their one and three year assessment. Seventy - five percent of scans were done

after day seven. Of the 10 scans done before day seven, three were abnormal with signs of cerebral oedema, two of which on repeat scanning were normal. These 10 infants were all normal at one year of age. There were 11 infants in total who had evidence of cerebral oedema on ultrasonography. Four of these developed cerebral palsy and it is possible that late subcortical leucomalacia was missed. If this was so it would only add weight to the predictive values of SCL on ultrasonography and would not affect the rest of the results.

In keeping with other developing countries (Airede and Weerasinghe, 1995)) severe asphyxia occurred commonly in the study population. The cause is not clear but is probably due to poor progress of labour resulting from a combination of an inadequate pelvis and a large infant. Other investigators have also suggested a maternal trace element deficiency which predisposes the infant, even in a normal labour process, to the effects of hypoxia (Harrison et al, 1998). Table 5.II shows a relatively low caesarean section rate which may have bearing on the severity of the cases included in this cohort. We had a high incidence of SCL in this cohort. It must, however, be appreciated that this is not a prevalence study but a study of the usefulness of a clinical assessment. Therefore the whole spectrum of HIE is represented.

Predictive values were used in evaluating the usefulness of neurological assessments as described by other workers in this field (Swanson et al, 1992; Allen and Alexander, 1994). Predictive values are more meaningful than sensitivity and specificity because they indicate the likelihood of disability. Sensitivity and specificity express retrospective relationships (De Groote, 1993).

Figure 5.1 indicates that there is a peak in mean score values on day three and day four. The predictive values of the score have, therefore, been determined on these days (Table 5.III) as well as for day seven and for the individual maximum score. The maximum score for each individual infant yielded a higher predictive value than that for day three or day four.

Evaluation of the infant on day seven , as other authors have found, is a useful time with regard to prognosis (Amiel-Tison and Ellison, 1986). Sarnat and Sarnat also indicated that normality after day six automatically placed an infant into the mild and therefore low risk group. Our highest predictive values were at this time. Predictive values were not re-evaluated at three years of age as the spectrum of abnormality had not changed and numbers were small.

The predictive values of the score are high, especially when the peak score and length of persistence of abnormal signs are considered together. Predictive values of 92% and 100% and sensitivities and specificity's of 100% and 93% respectively are excellent and higher than that of CT scanning in the study by Lipper et al (1986).

At one year of age it is difficult to assess mild ID but a DQ of 70 was taken as the cut off. We have described outcome in terms of normality or abnormality. There was one infant with a suspect neurological examination who had a normal DQ. He was placed in the normal group for the purpose of analysis. This child was unfortunately lost to follow-up at three years. He was likely to be ID.

Robertson and Finer (1993) have also defined perinatal variables useful for predicting good outcome in the moderate encephalopathy group and suggest that infants in this category can be discharged at an early age from follow-up. It is proposed that this score can be used to categorise infants into a low risk category thus allowing for health care workers working distant from tertiary medical centres the ability to decide which infants they can safely discharge from their overcrowded clinics. Use of the graphical representation of the cohort (Fig 5.1) may allow the rural clinician to superimpose the patient's profile and thereby predict outcome or allow discharge from follow-up.

The children assessed as normal at one year were all still normal at three years. No further children with intellectual disability were detected. There is a possibility that some ID was present in the children not seen but of those families traced (five of nine) none indicated telephonically that there was any problem. Some authors have suggested that even in the normal group there will be a gradation of DQ correlating with severity of HIE (Robertson and Finer, 1993; Saloojee and Cooper, 1994). These results do not show this trend, although numbers are too small to confirm a relationship between three year DQ and the maximum HIE score.

5.5 Conclusions

In conclusion, the HIE scoring system that has been adapted for the needs of the service within the PMNS and which has become an integral part of the care of the encephalopathic infant is:

1. Easy to use and can be adequately applied by junior staff members.
2. Correlates with the Sarnat and Sarnat descriptive grading
3. Has a high predictive value for outcome.

Certainly the parents of an asphyxiated infant who scores a maximum of 10 or less and is normal by day seven can be assured of a normal outcome. Those infants whose score peaks higher than 15 and who remain abnormal after day seven must have a guarded prognosis.

For the infant with HIE in this centre 40% of survivors have evidence of neurodevelopmental disability, mainly cerebral palsy. There was a high mortality rate in the disabled survivors from this cohort. Infants who appear normal at one year of age are likely to remain normal. The severity of the HIE in normal survivors does not apparently affect the DQ in this cohort although with the small numbers involved this conclusion must be drawn with circumspection.

Chapter 6.

Screening for neurodevelopmental problems in the neonatal period.

Screening for neurodevelopmental problems in the neonatal period

6.1 Introduction

It is not feasible to provide early neurodevelopmental intervention to all very low birthweight (VLBW) survivors because of the large numbers due to their increased survival (Fanaroff et al, 1995) and the fact that most preterm infants do not develop major disabilities (Escobar et al, 1991). There is a need, therefore, to target those infants likely to experience developmental disabilities so that they can benefit from early intervention. Scant resources must be focused on those with long-term needs. In order to do this, a reasonably efficient and reliable method of infant assessment is required.

The aim of this study was to evaluate the Dubowitz Neurological Assessment (DNA)(Dubowitz and Dubowitz, 1981), a Perinatal Risk Rating (PRR)(adapted from Molteno et al, 1995) and the Infant Neuromotor Assessment (INA)(Magasiner et al, 1997) separately and sequentially using a cohort of neonatal intensive care unit (NICU) graduates. This hopefully would offer a realistic prognostic tool for counselling of parents and would target early intervention where necessary.

6.2 Method

The cohort

A prospective follow-up study involving graduates from the Groote Schuur Hospital NICU was conducted. A cohort of 130 consecutive neonatal intensive care graduates were selected according to the high risk criteria as listed in Table 6.I. Each infant was examined with the DNA at term gestational age (as assessed by the Ballard score) and scored according to deviant items as described by Molteno et al (1995). Term infants in the cohort were assessed with the DNA on the day of hospital discharge or at 44 weeks gestational age, whichever came sooner.

The infants were classified as follows:

1. No deviant signs
2. 1 deviant sign
3. 2-3 deviant signs
4. 4 or more deviant signs.

Each infant was also allocated a PRR (Table 6.I). The level of risk was assigned according to the highest risk event in the perinatal course. Cranial ultrasound examination was carried out on each infant. In the case of term infants with HIE, ultrasound was usually carried out twice: within 48 hours of birth and on the day of hospital discharge or at two weeks of age, whichever came first. In preterm infants, ultrasound examination was done at the end of the first week of life and, if abnormal, repeated weekly until hospital discharge. The ultrasound result was recorded as the worst picture seen.

Table 6.I : Perinatal Risk Rating

Risk category	Risk Rating
Birthweight 1000-1499g; RDS; asphyxia neonatorum; symptomatic hypoglycaemia; recurrent apnoea	1
Birthweight 750-999g; IVH grade I & II; BPD, HIE without seizures	2
Birthweight <750g; IVH grade III & IV, PVL or SCL; seizures	3
Syndromes associated with intellectual disability; major CNS abnormality.	4

After discharge the infants were seen at 18 weeks of age (corrected) when the INA was carried out. This assessment was also scored according to deviant items (Magasiner et al, 1997). The cohort was seen again at one year corrected age and assessed by neurological examination and the Griffiths' Scales of Mental Development (Griffiths, 1976).

For the purposes of analysis, an infant was considered abnormal if there were clinical signs of cerebral palsy or intellectual disability (defined as a Griffiths' corrected developmental quotient less than 70).

Data analysis:

Data were recorded and analysed using the Epi Info program. Sensitivity, specificity and predictive values (Altman, 1991) were calculated for each assessment modality in order to evaluate their clinical usefulness. The positive predictive value indicates the ability of the assessment to predict abnormal outcome.

6.3 Results

130 infants who met criteria for the GSH follow-up program formed the cohort.

Perinatal data and outcome to term gestational age:

The characteristics of the cohort are shown in table 6.II. Eighty percent were preterm infants with a mean birthweight of 1172 g and a mean gestational age of 34 weeks. The remainder of the cohort comprised term infants who suffered perinatal hypoxia. The morbidity parameters are shown.

On Dubowitz assessment (Table 6.III) 84% of the cohort was normal (0 or 1 deviant sign), 9% had 2-3 deviant signs and 8% had 4 or more deviant signs. On PRR 85% were low risk (PRR = 1 or 2) and 15% high risk (PRR = 3 or 4) for developmental problems.

Table 6.II : Characteristics of the cohort - Morbidity

	Number n = 130	Percent	Range
Birth weight (mean)	1439g		580g - 3400g
Gestational age (mean)	34 wks		26 - 42 wks
Preterm	98	80%	
weight (mean)	1172g		580g - 2300g
gestation (mean)	34		26 - 36.8 wks
Sex	65 male	53%	
Ventilated (mean)	4 days	25%	1 -21 days
Oxygen required (mean)	8 days	56%	1 -99 days
BPD	6	5%	
Apnoea	15	12%	
NEC	7	6%	
Seizures	9	7%	
Cranial ultrasound			
IVH: Gr II	13	11%	
Gr III (with shunt)	2	1.6%	
Gr IV	2	1.6%	
PVL	4	3.3%	
SCL	2	1.6%	

Table 6.III : Assessment of the cohort at term gestational age

	Number n = 130	Percent
Dubowitz:		
0-1 deviant	109	84%
2-3 deviant	11	9%
4 or more deviant	10	8%
Perinatal Risk Rating:		
1	55	42%
2	55	43%
3	16	12%
4	4	3%

Outcome at 18 weeks corrected age and one year of age: Table 6.IV

Of the 130 infants, three died after 18 weeks but were known to be abnormal (two had CP with ID and the third was an infant with Down syndrome). A further two died during infancy with their neurodevelopmental status unknown at the time of death. Five children left the area before they reached one year of age. Contact was maintained with their families and none appeared to have a disability. Of the remaining 120 infants, 112 were assessed on the Griffiths Scales of Mental Development and neurological examination and six were assessed at home on a developmental screening test. Two other infants, both with known CP were unable to complete a formal Griffiths assessment but underwent neurological examination. For the analysis of outcome, data was used from the 120 evaluated after one year of age (112 Griffiths', six screened at home and two CP) plus the three deaths where the developmental status was known.

By 18 weeks of age six infants were diagnosed as having CP and six were developmentally delayed. A further 26 infants had 2 or 3 deviant signs on INA at this age and were regarded as suspect. Ninety two infants (71%) were normal.

At one year of age 111 (90%) infants were normal, three infants were developmentally delayed (one global delay, two specifically motor delay) and six infants had CP. Five infants died (two CP, one Down syndrome, two developmental status unknown). There were eight infants with CP in total over the 12 month period, only two of whom had a DQ above 70. Five infants had an abnormal DNA as well as a high PRR and seven of the eight were abnormal at their 18 week assessment. Other than the infants with CP, only one infant in the cohort had a DQ less than 70.

Table 6.IV : Outcome of infants at 18 weeks corrected age and one year of age

	18 weeks corrected age (n= 130)	One year
Lost	0	5
Died	0	5*
Normal	92	111
CP	6	6
DQ < 70	0	1
Developmental delay	6	2
Suspect	26	0

* Two CP infants, one Down syndrome and two unknown developmental status

Analysis of PRR and DNA:

The PRR was grouped as follows:

1 and 2 = low risk

3 and 4 = high risk.

The DNA was evaluated as follows:

0 - 1 deviant signs = normal

2 - 3 deviant signs = suspect

4 or more deviant signs = abnormal.

For analysis and evaluation of the best predictive value the DNA was grouped in two ways:

Group 1. Normal vs suspect + abnormal

Group 2. Normal + suspect vs abnormal

Table 6.V: Predictive values for normal one year outcome

	PPV%	NPV%	Sensitivity%	Specificity%
PRR	42	98	80	90
DNA Group 2	56	96	50	97
DNA Group 1	26	99	90	77
INA Group 2	82	99	90	98
INA Group 1	25	99	90	76

The Perinatal Risk Rating had a NPV of 98% (i.e. of infants with a PRR<3 98% will be normal at one year of age). Analysis (Table 6.V) showed the best predictive values for outcome at one year

of age of the Dubowitz Neurological Assessment were obtained using group two and was 96% (NPV) and 56% (PPV).

In order to evaluate the usefulness of the INA the infant outcome was grouped in the following ways:

Group 1. Normal (0-1 deviant signs) vs all abnormalities (2 or more deviant signs)

Group 2. Normal plus suspect (0-3 deviant signs) vs abnormals (4 or more deviant signs)

The highest predictive values were obtained using group 2. The Infant Neurological Assessment at 18 weeks of age is 99% predictive of normal outcome (NPV) at one year of age if 3 or less abnormal signs are present. The positive predictive value of abnormal outcome of the INA at 18 weeks is 82% if 4 or more abnormal signs are present.

6.4 Discussion

A number of scoring methods for identifying infants at risk for poor neurodevelopmental outcome have been proposed. Most of the early methods focused on specific complications that occurred during the perinatal period (Hobel et al, 1973). Subsequently a more global view was adopted, based on the amount of intensive care required (Salamy et al, 1988). A more direct approach assessed the potential effect of insults on the central nervous system by focusing on mechanisms of brain injury such as hypoxia, hypoglycaemia and hyperbilirubinaemia (Brazy et al, 1991).

The Neonatal Medical Index (NMI) of Korner et al (1993) combining birthweight and neonatal complications in a single score aims at predicting the intellectual and motor development of low birthweight, preterm infants up to three years of age, while the Neonatal Health Index (NHI) developed by Scott et al (1989) is a measure of neonatal health based on the length of hospital stay adjusted for birthweight, standardised to have a mean score of 100 and a standard deviation of 16.

The majority of studies on prediction deal specifically with low birthweight or preterm infants. For clinical practice, a system should include both VLBW and term asphyxiated infants (Molteno et al,

1995). Molteno et al developed a perinatal risk rating based on the neonatal clinical course and cranial ultrasonography findings. This rating, which is simple to apply and is applicable to both preterm and term infants, was used in the present study. As in the original study, it was found to have a high NPV but only a moderate PPV.

Allen and Capute (1989) used a method with items drawn from a number of sources to evaluate the outcome of VLBW infants. They found a good correlation between neonatal examination and neuromotor status at one year, but prediction of intellectual disability was less accurate. They concluded that although an abnormal examination could not be used to diagnose disability in preterm infants, it identified a group of high risk infants who should be carefully monitored during infancy and childhood.

Most early neonatal neurological examinations were designed for use in either preterm or term infants but not both. Dubowitz and Dubowitz (1981), however, developed one examination which could be used for preterm as well as full term neonates. They did not quantitate the items collectively nor give a single score, but looked at the number of deviant signs, showing that the greater the number of deviant signs, the greater the likelihood of later abnormality (Dubowitz et al, 1984). Molteno et al (1995) developed objective criteria for assessing deviant items on the Dubowitz examination and showed predictive validity in terms of neurodevelopmental outcome. Their study provided the method for evaluating deviant items in the present study. The Dubowitz Neonatal Neurological Assessment was accurate in predicting normal outcome in infants with 0 or 1 deviant sign, but less successful in detecting abnormal infants.

A number of tests of infant motor development have been described (see page 27, "Early infant assessment"). All these tests have been criticised and none generally accepted for clinical use. The INA was developed for screening infants referred to the follow-up clinic at Groote Schuur Hospital. It has been shown to be easily mastered by both medical and allied professions and could be completed within 10-15 minutes (Magasiner et al, 1997). The INA was used in the present study and its predictive validity confirmed.

6.5 Conclusions

The Dubowitz Neurological Assessment was shown to be useful in screening high risk infants for potential neurological abnormalities. The Perinatal Risk Rating was equally accurate and is far less time consuming. It can be applied by any staff member but the limitation of the PRR is that an ultrasonographic examination of the newborn brain is required. In a rural or secondary level hospital infants can be screened with the DNA at hospital discharge. In a tertiary level hospital the PRR is sufficient.

We have also shown the INA at 18 weeks to be a sensitive screening examination for infants at risk and this assessment can be used effectively at community based clinics. Infants demonstrating four or more deviant signs at 18 weeks of age should be referred to a tertiary centre for neurodevelopmental therapy (NDT) and further follow-up.

The following management protocol is recommended:

At discharge:

1. If the PRR is low (1 or 2) or the DNA is normal (0-1 deviant signs) the infant can be followed up in the community by 'well infant' services.
2. If the PRR is high (3) or if the DNA is abnormal (4 or more deviant signs) the infant should be seen at 18 weeks of age for an INA.
3. If the PRR is equal to 4 then the infant should be referred immediately for NDT and follow-up.

At 18 weeks:

1. If the INA is normal (0-1 deviant signs) the infant can be discharged to follow-up by community 'well infant' services.
2. If the INA is abnormal (4 or more deviant signs) the infant should be referred for NDT and follow-up by a multidisciplinary developmental clinic.
3. If the INA is suspect (2-3 deviant signs) the infant should be seen at six to nine months for a repeat INA and re-evaluation.

Chapter 5

Conclusions and recommendations

Of the VLBW infants (less than 1250g), 61% survived to discharge from hospital. In the case of infants weighing less than 1 000g, 42% survived, whereas for those over 1 000g the survival rate was 83%. Better survival was documented for infants of mothers who attended antenatal care, for infants who weighed more than 900g and infants who were older than 30 weeks gestation. The majority of infants in this study were UGA and stunted. Gestational proteinuric hypertension had a protective effect possibly, because it necessitated hospital care. Twenty seven percent of infants were ventilated of whom half survived. Eleven infants died in the first six months after discharge.

Approximately 10% of the VLBW infants in this study developed some form of disability, with most manifesting cerebral palsy. No children were blind or deaf. Clinical neurodevelopmental assessment was found to be accurate at 18 weeks corrected age in detecting infants with suspected CP. The Griffiths Scales of Mental Development were useful from two years of age when it became possible to detect those children with intellectual disability. The score uncorrected for gestational age tended to overestimate the number of children without cerebral palsy who were intellectually borderline at two years of age. Use of the corrected score up to the age of two years seems more appropriate. Pre-school assessment identified a number of children who were likely to have learning problems. Control children were far less likely to have similar problems.

The HIE scoring system, applicable for the term newborn with perinatal hypoxia in the neonatal period, proved predictive of neurodevelopmental outcome. The best correlation with outcome was a combination of the peak score and evaluation on day seven; with a peak score more than 15 and a score more than one on day seven the positive predictive value was 92% and the negative predictive value was 100% for abnormal outcome, with a sensitivity of 100% and specificity of 93%. The HIE score is easy to use and correlates with the Sarnat and Sarnat

descriptive grading. An asphyxiated infant whose score peaks higher that 15 and who remains abnormal after day seven must have a guarded prognosis. On the other hand when an infant scores a maximum of 10 or less and is normal by day seven, the parents can be virtually assured that their infant will have a normal outcome.

Of the infants with HIE who survived the neonatal period, approximately 42% developed neurodevelopmental disability. Most of these abnormal infants had cerebral palsy and six of 16 cerebral palsied infants died during infancy. The presence of seizures had a positive predictive value of 57% for an abnormal outcome, with a negative predictive value of 92%. In other words, an infant with HIE who did not have a seizure had a 92% chance of being normal. An abnormal cranial ultrasound examination was highly predictive of abnormal outcome in that all of the infants who had subcortical leucomalacia on ultrasound developed cerebral palsy.

In a cohort of NICU survivors both the Dubowitz Neurological Assessment and the Perinatal Risk Rating at term gestational age were predictive of outcome. At 18 weeks corrected age the Infant Neuromotor Assessment was predictive of normality and sensitive for the detection of cerebral palsy.

For the high risk infant at the time of discharge from hospital, there are a number of follow-up options:

1. Routine developmental screening at the community clinics, carried out by community health nurses
2. Follow-up at the nearest MOU, by a visiting doctor
3. Follow-up at the tertiary hospital, by a developmental specialist using the INA
4. Referral to a multidisciplinary developmental or cerebral palsy clinic at the tertiary referral hospital for ongoing treatment and follow up.

Infants can be categorised according to the degree of risk for neurodevelopment disability as follows:

1. **Low risk:**
   - birthweight 1500g or more and no major risk factor as listed below

2. **At risk:**
   - birthweight between 1000 g and 1500g
   - cranial ultrasonography normal or IVH grade 1 or 2
   - asphyxia neonatorum
   - HIE with a peak score less than 15 and a score of zero by day seven, without seizures
   - symptomatic hypoglycaemia
   - DNA: 1 - 2 deviant signs

3. **High risk:**
   - birthweight less than 1000 g
   - cranial ultrasonography IVH grade III or IV or leucomalacia
   - HIE with a peak score more than 15 or score more than zero on day 7
   - seizures regardless of cause
   - DNA: 3 - 4 deviant signs

4 **Abnormal:**
   - syndromes associated with disability, or microcephally
   - clinical neurological abnormality with or without cranial ultrasound showing hydrocephalus or porencephaly
   - DNA: 4 or more deviant signs

The proposed follow-up plan is as follows:

A. Low risk infants should be screened at the community clinics. Referrals from here to a multidisciplinary developmental or cerebral palsy clinic at the tertiary referral hospital would follow the same path as any other community referral.

B. At risk infants should be seen at the MOU's where they would be evaluated by a visiting doctor. Any problem or query could be referred back to the developmental specialist at the tertiary hospital.

C. High risk infants should be evaluated at 18 weeks corrected age with the INA by a developmental specialist at the tertiary hospital follow-up clinic. If the INA is normal (0 - 1 deviant sign) the infant can be referred for community follow-up. A suspect examination (2 -3 deviant signs) would indicate the need for review at six to nine months. Neurodevelopmental therapy or guidance would be helpful in the intervening period. In the case of an abnormal examination (4 or more deviant signs) referral to a multidisciplinary developmental or cerebral palsy clinic at the tertiary referral hospital for therapy and follow-up would be indicated.

D. Abnormal: Any infant with established neurodevelopmental disability identified in the neonatal period or at follow-up should be referred to a multidisciplinary developmental or cerebral palsy clinic at the tertiary referral hospital for treatment and long-term follow-up.

At risk and high risk infants who do not manifest disabilities at follow-up are advised to attend pre-school centres from the age of four years. This will enable minor disabilities to be detected and managed as soon as they appear. Parents should also be encouraged to seek help from the developmental specialists at any stage should they have concerns regarding their child's developmental progress.

This study has evaluated the outcome of the high risk infant in the PMNS. It has provided valuable audit of outcome from the NICU at Groote Schuur Hospital. Extrapolation of the data from this NICU can give the health care planner an idea of the level of need for the disabled VLBW survivor in Cape Town. It has delineated the extent of the impact of being VLBW into the pre-school years and has exposed the magnitude of possible learning disability in these children. It is hoped that this data will provide an increased awareness of the needs of the VLBW infant and encourage early and ongoing assessment.

It has evaluated several methods of early infant neurodevelopmental assessment and has demonstrated the effectiveness of the Dubowitz Neurological Assessment, the Perinatal Risk Rating, and the Infant Neuromotor Assessment in detection of suspected cerebral palsy. From this early assessment affected infants can be referred to appropriate services for ongoing management of their problems.

The infant with HIE has been evaluated and although the data does not constitute a prevalence study it does indicate how much this condition may be adding to the burden of disabled children in the city of Cape Town. It must provide the impetus for a thorough investigation into the incidence and epidemiology of this condition in Cape Town.

The value of the HIE score in the assessment of these infants has been demonstrated and its consistent use in the PMNS will provide clinicians with an accurate indication of the need for close follow-up of these infants and early detection of developmental problems.

Cape Town's place in South Africa, and South Africa as a prominent member of the developing countries could allow this data to become an example to others. The use of the early evaluation methods illustrated in this work could apply to other countries and would improve ongoing care of the high risk infant in the developing world. The VLBW infant contributes to the high risk infant in Africa, but the plight of the infant with HIE also deserves urgent and thorough attention. This often avoidable condition warrants vigorous efforts from the research community in South Africa to establish its incidence, prevalence and to evaluate prevention and rescue strategies.

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Appendices - List of abbreviations

Apn	Apnoea and management
ADH	Attention deficit and hyperactivity
BPD	Bronchopulmonary dysplasia
BW	Birthweight
C No	Case number
Deliv	Delivery type
D/CD	Death post discharge
Dub	Dubowitz assessment at term gestational age
Dvent	Days ventilated
DysD	Days until death
D1	HIE score on day one (same for D2, D3 etc)
ENND	Early neonatal death
F	Female
FAS	Fetal alcohol syndrome
G	Gravidity
GA	Gestational age
GQc	General quotient - corrected for gestational age
GQu	General quotient - uncorrected for gestational age
HC	Head circumference at six years of age
Ht	Height at six years of age
HrsD	Hours until death
Hypo	Hypoglycaemia and severity
INA	Infant Neuromotor Assessment
Inst	Instrumental delivery
IVH	Intraventricular haemorrhage - grades
LNND	Late neonatal death
M	Male
Mage	Maternal age
NEC	Necrotising enterocolitis
Norm	Day on which infant became normal
O2/V	Oxygen and ventilation requirements
P	Parity
Pneum	Pnemonia in perinatal period
PNND	Post neonatal death
PnThx	Pneumothorax
PRR	Perinatal Risk Rating
Resus	Resuscitation required
ROP	Retinopathy of prematurity - grades
Score	HIE score

Sresp	Time to spontaneous respiration
UGA	Underweight for gestational age
U/S	Cranial ultrasound result
Wt	Weight at 6 years of age
1m	Apgar at 1 minute
5m	Apgar at 5 minutes
1Yr	Assessment at one year

Appendix 4.I: Questionnaire for VLBW study - survivors

NAME: < >

ADDRESS: < >

AREA CODE: ####

NUMBER: #########

BIRTH DATE: <mm/dd/yy>

BIRTH WEIGHT: #### grams

IUGR: <y>

HEAD CIRC: ##.# cms

SCORED GEST: ##.# weeks

MAT GRAVIDITY: #

MAT PARITY: ###

MAT AGE: ## years

VDRL: #
1=neg
2=pos,untreated
3=pos,treated
4=no result

BLOOD GROUP: #
1=O pos
2=O neg
3=A pos
4=A neg
5=B pos
6=B neg
7=AB pos
8=AB neg

ANTIBODIES: <y>

CHRONIC ILLNESS: <y>

If yes < >

FAMILY HISTORY: <y>

If yes < >

DRUGS: #
1=no
2=yes,medicinal
3=yes,abuse

If yes < >

ALCOHOL: #
1=never
2=stopped
3=social
4=moderate
5=heavy

SMOKING: #
1=never
2=stopped
3=moderate
4=heavy

TORCH INFECTIONS: #
1=nil
2=Toxo
3=Syphilis
4=Rubella
5=CMV
6=Herpes

ANTENATAL: #
1=normal

2=GPH
3=Abruption
4=GDM
5=other

If other < >

TYPE OF PREGNANCY: # 1=singleton
2=twins
3=triplets

DELIV/PRES: # 1=NVD
2=Vag,breech
3=C/S,vertex
4=C/S,breech
5=C/S,transverse
6=hand
7=shoulder

MEMBRANES RUPTURED:## hours

MEC STAINED LIQ: <y>

FORCEPS: # 1=nil
2=Neville Barnes
3=Kiellands
4=Wrigley

CORD PROLAPSE: <y>

APGAR SCORE 1 min ##

5 min ##

10 min ##

SPONTANEOUS RESP ## Mins

CORD pH: #.##

CORD BE: #.##

RESUS: # 1=nil
2=O2 only
3=mask
4=mask + narcan
5=Intubation
6=Intub. + narcan
7=Int,narcan,dex,NaBic

PCV at birth: ##

BUBBLES: # 1=neg
2=intermediate
3=pos
4=not done

GRAM: # 1=not done
2=neg
3=pus cells only
4=orgs only
5=pus + orgs

ORGANISMS: # 1=nil
2=G pos
3=G neg
4=both

URINE GBS: # 1=not done
2=neg
3=pos

RHUEMATOID FACTOR: # 1=not done
2=neg
3=pos

CONGEN SYPHILIS: <y>

CONGEN INFECTION: <y>

FETAL ALC SYNDROME:# 1=considered
2=no
3=yes

BLOOD TRANSFUSION: <y>

NUMBER OF BTF: #

PCV PRIOR TO BTF: ##
##
##

RESPIRATORY PROBS: # 1=nil
2=HMD
3=TTN
4=Pneumonia
5=BPD
6=other

If other< >

PNEUMONIA: # 1=G pos
2=G neg
3=nil isolated

PNEUMOTHORAX: # 1=nil
2=unilateral
3=bilateral

MANAGMT RESP PROBS:# 1=nil req'd
2=HBox
3=nasal prongs
4=CPAP
5=Ventillation

DAYS VENTILLATED: ##

MAX FiO2: ##

MAX PRESSURE: ##.#

APNOEA: # 1=no
2=yes,no active Mx
3=yes,CPAP
4=Yes,ventillated

CONGEN HEART DIS: # 1=no
2=PDA
3=VSD
4=other

If other< >

COMPLICATIONS: # 1=nil
2=CCF

IF PDA PRESENT: # 1=nil
2=indocid
3=ligation

NNJ: # 1=no
2=photoRx
3=exchange

MAX TSB: ###

INFANT BLOOD GROUP:# 1=no record
2=O +
3=O -
4=A +
5=A -
6=B +

7=B -
8=AB +
8=AB -

COOMBS: # 1=no record
2=neg
3=pos

NEC: # 1=nil
2=yes,no Cx's
3=yes,req'd surgery

OTHER GIT: <y>

If yes< >

IVH: # 1=nil,U/S done
2=nil,no U/S
3=gr 1
4=gr 2
5=with hydrocephalus(gr 3)
6=gr 4
7=req'd shunt

CONGEN HYDROCEPH: <y>

CONVULSIONS: <y>

If yes cause< >

RETINOPATHY: <y>

GRADE OF RET: #

MUSCULOSKELETAL: <y>

SKIN ABN: <y>

HYPOTHERMIA: <y>

HYPOGLYCAEMIA: <y>

INFANT OF DIABETIC:<y>

MAT DIABETIC TYPE: # 1=non gest. DM
2=gest DM

MAT TREATMENT: # 1=diet
2=oral
3=insulin

INFANT TREATMENT: # 1=feed
2=IVI 10% dextrose
3=steroids

AFIS: <y>

ORGANISM: # 1=not isolated
2=G +
3=G -
4=both

DISCHARGE DATE: <mm/dd/yy>

WEIGHT: #### grams

HEAD CIRC: ## cms

TERM EVAL DATE: <mm/dd/yy>

EVALUATION: #

If abnormal< >

SIX WEEKS DATE: <mm/dd/yy>

WEIGHT: #### grams

HEAD CIRC: ## cms

FEEDS: #
SMILING: <y>
FOLLOWING: <y>
HEARING: #
PROBLEMS SINCE D/C: <y>
If yes< >
GEN EXAM: #
If abnormal< >
MOLTENO ASSES: #
If abnormal< >
PHYSIO ADVICE: <y>
TRANSPORT COSTS: #.##

EIGHTEEN WK DATE: <mm/dd/yy>
WEIGHT: #### grams
HEAD CIRC: ## cms
FEEDS: #
PROBLEMS SINCE 6W: <y>
If yes< >
SMILING: <y>
FOLLOWING: <y>
PLAYS W FINGERS: <y>
PLAYS W FEET: <y>
GRASPS RING: <y>
TURNS TO SOUND: <y>
ROLLS PRONE TO SUP: <y>
ROLLS SUP TO PRONE: <y>
HAND TO MOUTH: <y>
LAUGHS ALOUD: <y>
GEN EXAM: #
If abnormal< >
MOLTENO ASSES: #
If abnormal< >
PHYSIO ADVICE: <y>
TRANSPORT COSTS: #.##

NINE MONTH DATE: <mm/dd/yy>
WEIGHT: #### grams
HEAD CIRC: ## cms
MIXED DIET: <y>
PROBLEMS SINCE LAST:<y>

If yes< >
GEN EXAM: #
If abnormal< >
MOLTEMO ASSES: #
If abnormal< >
PHYSIO ADVICE: <y>
TRANSPORT COSTS: #.## Rand
ONE YEAR DATE: <mm/dd/yy>
DEFAULT: <y>
DEFAULT STATUS: < >
WEIGHT: #####g
HEAD CIRC: ##cms
MOLTENO NORMAL: <y>
CEREBRAL PALSY: <y>
DEVELOPMENTAL DELAY:<y>
CLINICAL DETAILS: < >
GRIFFA: ###.#
GRIFFB: ###.#
GRIFFC: ###.#
GRIFFD: ###.#
GRIFFE: ###.#
GENERAL QUOTIENT: ###.#

CONTACT PHONE: ########
CONTACT ADDRESS: < >
Seen at one year: <Y>
Hosp adm yr 1: ##
Hosp adm yr 2: ##
Chronic illness: <Y>
Details:

Convulsive disorder: <Y>
Details:

ROP: <Y>
Seen at two years: <Y>
LTFU: <Y>
Age lost (months): ##
Chron age at griff2 (months): ##.#

Corr age at griff2 (months): ##.#

Weight (Kg's): ##.#

Head circ (cm's): ##

Gen exam: #

Details if abnormal:

Iatrogenic scars: <Y>

Scar details:

Hearing: #

Molteno asses: #

Molteno details:

Griff2 A: ###

Griff2 B: ###

Griff2 C: ###

Griff2 D: ###

Griff2 E: ###

Griff2 F: ###

Griff2 GQ: ###

Chron2 A: ###

Chron2 B: ###

Chron2 C: ###

Chron2 D: ###

Chron2 E: ###

Chron2 F: ###

Chron2 GQ: ###

Griff1 GQ: ###

Chron1 A: ###

Chron1 B: ###

Chron1 C: ###

Chron1 D: ###

Chron1 E: ###

Chron1 GQ: ###

Parents married: #

Income: #

{DOT} <dd/mm/yy>

{DOB} <dd/mm/yy>

{CA} ##.##

{Time} _

{Studypop} _

{5yWeight} ##.##

5yHeight} ###.##

{5yHeadcirc} ##.##

PARENTAL PERCEPTION AND AWARENESS

{DIFFNOT} _ {GROSSMOTPR} problem _ {FINMOTPR} problem _

{DRAWEXP} _ {DRESSING} problem _ {EATING} problem _

{HYPER} _

{HELP} sought if problem noted _

{DESCRIBBEH} _____

_____

GRIFFITH at 6 years:

{LOCOMOT}DQ ### {PERSSOC}DQ ### {HEARSPEECH}DQ ###

{EYEHAND}DQ ### {PERFORM}DQ ### {PRACREASON}DQ ###

{GRIFFDQ} ###

{GENCOM} general comments and recommendations

_____

{Attention deficit} _

C No	BW	M/F	UGA	GA	Mage	Deliv	Inst	Sresp	Resus	FAS	Pneum	PnThx	O2/VD	Vent	BPD	Apn	NEC	IVH	ROP
1	1240	F	Y	33	30	3	1	1	1	2	0	1	2	0	N	1	1	1	0
2	1050	F	Y	33.2	25	3	1	1	1	2	0	1	5	7	Y	1	1	1	0
3	1190	F	Y	35	24	1	1	1	1	2	0	1	1	0	N	2	1	2	0
4	1230	M	N	30	16	1	1	1	2	2	0	1	2	0	N	1	1	1	0
5	1170	M	Y	32.4	28	3	1	1	3	2	0	1	2	0	N	1	1	1	0
6	720	M	N	26.8	22	1	1	1	2	2	3	1	5	6	Y	1	1	4	0
7	1245	M	N	31.4	19	8	1	0	1	2	0	1	2	0	N	2	1	2	0
8	1240	M	N	30	34	3	1	1	2	2	0	1	2	0	N	1	1	2	0
9	1225	F	Y	40	22	8	1	0	1	2	1	1	5	7	N	1	1	1	0
10	940	F	Y	30	28	3	1	6	4	2	0	1	1	0	N	1	1	2	0
11	1060	F	Y	31	22	1	1	1	2	2	0	1	2	0	N	1	1	2	0
12	1245	F	N	28	19	3	1	5	5	2	0	1	5	3	N	1	1	1	0
13	1045	M	Y	31.6	28	1	1	5	5	2	1	2	5	19	N	1	3	8	.
14	1090	F	Y	33.2	27	1	1	0	5	2	0	1	1	0	N	1	1	3	1
15	1025	F	Y	37.2	28	3	1	1	1	2	0	1	1	0	N	1	1	3	0
16	1030	F	Y	35	31	3	1	8	5	2	0	1	2	0	N	2	1	2	0
17	880	F	Y	30	21	1	1	0	1	2	0	1	5	10	N	3	1	4	1
18	1145	M	Y	33.6	32	3	1	7	6	2	0	1	1	0	N	1	1	1	0
19	1070	F	Y	35.8	24	3	1	1	3	2	0	1	1	0	N	1	1	2	0
20	1100	M	Y	32.8	33	3	1	5	7	2	0	1	2	0	N	1	1	2	0
21	1160	F	Y	32.8	17	4	1	5	2	2	2	1	5	23	N	1	1	1	.
22	1200	F	N	32	36	1	1	1	1	2	0	1	2	0	N	1	1	2	.
23	1010	F	N	30.8	16	1	1	0	3	2	0	1	2	0	N	2	1	3	0
24	1165	M	Y	31.6	16	1	1	3	6	2	2	1	2	0	N	1	1	1	0
25	870	F	Y	31.4	35	3	1	1	3	2	3	1	2	0	N	2	1	2	0
26	900	F	N	29	29	1	1	10	2	2	0	1	2	0	Y	1	1	4	0
27	1060	F	Y	32	21	3	1	7	5	2	0	1	2	0	N	1	1	2	0
28	900	F	Y	36.8	34	3	1	1	1	2	1	1	2	0	N	1	1	2	0
29	1190	F	N	31.2	35	1	1	0	2	2	0	1	1	0	N	1	1	2	0
30	1200	M	N	30	16	1	1	1	1	2	0	1	1	0	N	1	1	2	0
31	980	F	N	28.8	23	2	1	0	3	2	0	1	2	0	N	2	1	1	0
32	860	F	Y	30	38	1	1	0	3	2	0	1	2	0	N	1	1	2	.
33	990	M	Y	30	25	3	1	0	5	2	0	1	2	0	N	1	1	2	.
34	1050	M	N	29	34	3	1	1	2	2	0	1	2	0	N	1	1	1	0
35	980	M	Y	32.4	18	8	1	0	1	2	0	1	1	0	N	2	1	2	0
36	1095	F	N	30	26	3	1	10	6	2	1	1	5	7	N	1	1	1	0
37	880	F	Y	33	22	3	1	5	6	2	3	1	2	0	N	1	1	2	0
38	1245	M	Y	35.2	16	1	4	1	2	2	0	1	2	0	N	1	1	2	.
39	1230	F	N	31.8	20	2	1	4	5	2	1	1	5	3	N	1	1	2	0
40	1200	M	Y	34	30	1	1	1	2	2	0	1	1	0	N	1	1	2	0
41	1190	M	Y	33	26	3	1	1	1	2	0	1	1	0	N	1	1	2	0
42	1180	F	N	31.2	18	1	1	1	2	2	0	1	1	0	N	1	1	1	0
43	600	M	Y	35.8	21	3	1	1	1	2	0	1	4	24	N	3	2	1	0
44	1020	M	N	30	29	1	1	1	1	2	3	1	2	0	N	3	1	1	0
45	1060	F	Y	31.2	18	1	1	0	2	2	0	1	2	0	N	1	1	2	0
46	750	F	Y	30.8	34	1	1	1	2	1	3	1	4	0	N	3	1	1	0
47	940	M	Y	31	25	3	1	2	5	2	1	1	5	6	N	1	1	3	0
48	1050	F	Y	32	24	1	3	1	1	2	0	1	1	0	N	1	1	2	0
49	1200	F	Y	32.4	24	2	1	1	3	2	0	1	2	0	N	1	1	2	0
50	900	F	Y	30.8	32	1	1	5	3	2	0	1	2	0	N	2	1	2	0
51	930	M	Y	30	26	1	1	3	5	2	1	1	5	24	Y	1	1	3	.
52	1140	F	Y	35.2	35	1	1	0	3	2	3	1	2	0	N	2	1	1	0

C No	BW	M/F	UGA	GA	Mage	Deliv	Inst	Sresp	Resus	FAS	Pneum	PnThx	O2/VD	Vent	BPD	Apn	NEC	IVH	ROP
53	1200	M	N	31.2	19	2	1	4	5	2	0	1	2	0	N	1	1	2	0
54	1000	M	Y	33.6	28	3	1	1	1	2	0	1	2	0	N	2	2	2	.
55	1050	M	Y	34	32	3	1	1	1	2	0	1	2	0	N	1	1	3	0
56	1150	F	Y	32.8	19	1	1	1	1	2	0	1	1	0	N	1	1	1	0
57	1125	M	Y	33.6	26	3	1	22	5	2	0	1	2	0	N	1	1	2	0
58	1245	M	Y	35.2	35	3	1	1	2	2	0	1	1	0	N	1	1	2	0
59	1115	F	Y	32	21	8	1	1	1	2	0	1	4	2	N	3	1	5	0
60	915	M	Y	29.6	23	1	1	2	3	2	1	1	2	0	N	4	1	3	0
61	890	M	N	27	31	3	1	10	7	2	0	1	2	0	N	1	1	2	.
62	1210	F	N	31.8	30	3	1	12	7	2	3	1	2	0	N	2	1	2	0
63	900	F	Y	33.2	24	3	1	1	2	2	0	1	1	0	N	1	1	2	0
64	975	M	Y	34	37	8	1	0	1	1	3	1	2	0	N	1	1	3	1
65	1220	M	Y	36	35	1	1	1	2	2	0	1	1	0	N	1	1	2	0
66	1050	F	N	30	25	4	1	2	3	2	0	1	5	1	N	1	1	4	.
67	1245	M	Y	34	29	3	1	1	1	2	0	1	1	0	N	1	1	2	0
68	1210	M	Y	34.8	35	3	1	1	2	2	0	1	2	0	N	1	1	2	.
69	1245	F	Y	35.6	16	1	1	1	2	2	0	1	1	0	N	1	1	2	0
70	780	M	Y	28	26	1	1	0	5	2	1	1	5	12	N	4	1	6	1
71	1020	F	Y	32.4	21	1	1	0	1	2	3	1	5	2	N	1	1	1	0
72	850	M	Y	36.4	22	3	1	2	3	2	0	1	1	0	N	1	1	1	0
73	915	F	N	28	21	2	1	0	2	2	0	1	2	0	N	2	1	4	.
74	1030	M	Y	30.8	16	1	1	1	3	2	0	1	2	0	N	1	1	2	.
75	880	M	Y	29.6	31	1	1	1	1	2	0	1	2	0	N	2	1	1	.
76	1050	F	N	28	19	1	1	1	2	2	0	2	5	2	N	1	1	3	.
77	875	F	Y	34	19	3	1	6	5	2	0	1	2	0	N	1	1	2	0
78	1180	M	N	30	27	2	1	3	3	2	3	1	4	1	N	1	1	2	.
79	1100	F	N	28	15	2	1	1	3	2	0	1	2	0	N	1	1	2	0
80	1150	F	Y	34	28	1	2	0	6	2	1	1	5	4	N	1	3	4	0
81	1180	M	Y	33.8	33	4	1	8	6	1	0	1	2	0	N	1	1	1	.
82	910	M	N	28	38	1	1	0	1	2	0	1	4	0	N	3	2	1	0
83	885	F	Y	34	27	1	1	1	1	2	0	1	1	0	N	1	1	2	0
84	1120	M	Y	33.8	25	2	1	10	5	2	0	1	2	0	N	1	1	2	0
85	1195	M	N	30.5	32	3	1	1	2	2	0	1	2	0	N	1	2	2	0
86	1030	M	Y	34	32	1	1	1	2	2	0	1	1	0	N	1	1	2	2
87	1120	M	N	28.4	27	1	1	1	2	2	3	1	5	21	Y	2	1	3	0
88	1160	M	Y	37	26	3	1	1	2	2	0	1	1	0	N	1	1	2	0
89	840	F	N	28	40	2	1	1	3	2	0	1	2	0	N	1	2	3	0
90	840	F	Y	34.4	20	2	1	1	3	2	0	1	5	3	Y	2	1	5	0
91	990	F	Y	34.4	20	2	1	1	2	2	0	1	2	0	N	2	1	1	0
92	1010	M	Y	34.2	26	3	1	1	3	2	0	1	2	0	N	1	1	2	0
93	1120	F	N	31.6	18	3	1	1	1	2	0	1	1	0	N	1	1	2	.
94	1050	M	Y	36	28	3	1	1	2	2	0	1	1	0	N	1	1	2	0
95	1050	F	N	30.8	46	1	1	1	3	2	0	1	2	0	N	1	1	2	0
96	840	F	Y	30	28	3	1	3	5	2	3	2	5	2	N	4	1	8	.
97	1120	F	Y	33.6	31	2	1	5	5	2	4	1	5	12	Y	1	3	5	.
98	1180	M	Y	32	14	3	1	20	5	2	3	1	5	2	Y	1	1	2	0
99	1150	F	Y	33.6	24	3	4	0	3	2	0	1	2	0	N	1	2	2	.
100	900	M	Y	31	19	3	1	0	7	2	0	1	5	10	N	1	1	4	0
101	865	F	Y	30	27	3	1	5	5	2	3	1	5	2	N	1	1	2	0
102	1160	M	N	31.4	22	1	1	6	5	2	0	1	2	0	N	1	1	2	0
103	950	F	Y	32	28	1	1	2	6	2	0	1	4	0	N	3	2	3	.
104	1090	M	N	28	19	2	1	3	5	2	3	1	5	1	N	1	1	2	2

C No	BW	M/F	UGA	GA	Mage	Deliv	Inst	Sresp	Resus	FAS	Pneum	PnThx	O2/VD	Vent	BPD	Apn	NEC	IVH	ROP
105	1100	M	N	31	19	2	1	1	5	2	0	1	2	0	N	2	1	1	0
106	1175	F	Y	32.4	23	1	4	1	2	2	0	1	1	0	N	1	1	2	2
107	750	F	Y	30	26	1	1	5	2	2	0	1	2	0	N	2	1	3	2
108	1050	F	Y	31.6	21	1	1	1	2	2	0	1	2	0	N	2	1	1	.
109	1230	F	Y	34	17	1	1	1	1	2	0	1	1	0	N	1	1	2	0
110	1170	F	N	31.6	27	1	1	1	2	2	0	1	2	0	N	1	1	2	.
111	900	M	Y	31.6	25	1	1	8	5	2	3	1	2	0	Y	3	1	5	.
112	1145	M	Y	33.2	42	2	1	5	3	2	2	1	2	0	N	1	1	1	0
113	700	M	N	26.8	22	1	1	1	2	2	3	1	1	0	N	3	1	3	0
114	960	F	Y	34	29	1	1	1	2	2	0	1	1	0	N	1	1	1	0
115	1140	M	Y	32.8	33	4	1	6	5	2	0	1	2	0	N	2	1	3	0
116	930	M	Y	33.6	19	3	1	1	1	2	0	1	2	0	N	1	1	1	.
117	980	F	Y	32	24	3	1	16	6	2	0	1	4	0	N	1	1	1	0
118	1210	M	Y	32.8	28	2	4	2	2	2	1	1	2	0	N	2	1	1	0
119	1075	M	Y	33	41	4	1	1	2	2	3	1	2	0	N	2	1	2	0
120	1225	M	N	31.6	23	8	1	0	1	2	2	1	2	0	N	1	1	2	0
121	1010	M	Y	32	28	4	1	1	4	2	0	1	2	42	N	1	1	1	0
122	1200	M	Y	36	16	3	1	1	1	2	0	1	1	0	N	1	1	1	0
123	1200	F	Y	36	20	4	1	5	5	2	0	1	2	0	N	1	1	2	0
124	1240	M	N	28	24	1	1	5	5	2	4	1	5	3	N	2	1	1	.
125	880	F	N	29	21	1	1	1	2	2	0	1	5	4	N	1	1	1	0
126	800	F	Y	34	28	3	1	1	2	2	0	1	1	0	N	1	2	2	0
127	1000	M	Y	35.6	25	3	1	1	1	2	3	3	4	0	N	1	3	1	.
128	1170	M	Y	31.6	24	4	1	1	1	2	0	1	1	0	N	1	1	2	0
129	1210	M	N	29	28	1	1	0	3	2	0	1	2	0	N	1	1	2	0
130	785	F	Y	30	24	8	1	0	1	2	0	1	2	0	N	1	1	2	0
131	1190	M	N	32	25	1	1	1	1	2	0	1	5	1	N	1	1	2	0
132	790	M	Y	33.8	35	1	3	1	1	2	0	1	1	0	N	1	1	1	0

Appendix 4.III: Questionnaire for the VLBW study - deaths

(see VLBW study questionnaire - live infants for coding)

NAME: < >

Address: < >

Date of Birth: <mm/dd/yy>

Infant Folder No: ########

Sex: #

Date of Death: <mm/dd/yy>

Early Neonatal: <y>

Died at delivery: <y>

Late Neonatal: <y>

Post Neonatal: <y>

Death after discharge: <y>

Birth Weight: ####grams

IUGR: <y>

Head Circumference: ##.#cms

Gestational Age: ##.#weeks

Scored: <y>

Maternal Gravidity: ##

Maternal Parity: ####

Maternal Age: ##years

VDRL: #

Blood Group (maternal): #

Antibodies: #

Torch Infections: #

Antenatal Course: #

If Other: < >

ROM: ##hours

Meconium Stained Liquor: <y>

Type of Pregnancy: #

Mode of Delivery: #

Cord Prolapse: <y>

APGAR 1 minute: ##

APGAR 5 minutes: ##

APGAR 10 minutes: ##

Time Spont Respir: ## minutes

Cord pH: #.##

Cord BE: ##.#

Resusitation: #

PCV @ Birth: ##

Bubbles: #
Gr Stain of Gastric Asp: #
Urine GBS: #
Rheumatoid Factor: #
Cong Syph: <y>
Congenital Infection: #
FAS: #
Blood Transfusion: <y>
How Many: #
PCV Prior to Transfusion: ##
##
##
Respiratory Problems: #
If Other: < >
If Pneumonia: #
Pneumothorax: #
Management of RDS: #
Ventilation: ##days ##hrs
Max Oxy Conc: ###%
Maximal Pressure: ##.#
Apnoea: #
Congenital Cardiac Anomaly: #
If Other: < >
Complications: #
If PDA present: #
NNJ: #
Maximal TSB: ###
Blood Group: #
Coombs: #
NEC: #
Other GIT Problems: < >
IVH #
Congenital Hydrocephalus <y>
Convulsions: <y>
Aetiology of Convulsions: < >
Other CNS Problems: < >
Musculoskeletal Abnormality: <y>
If Yes: < >
Skin Abnormality: <y>
If Yes: < >
Hypothermia: <y>

Hypoglycaemia: <y>

IDM: <y>

Mother, Type of Diabetes: #

Treatment of Mother: #

Treatment of Infant: #

AFIS: <y>

Organism in AFIS: #

Age at Death: ## hrs ## days

Cause of Death: < >

PM Done: <y>

PM Findings: < >

C No	M/F	ENND	LNND	PNND	D/CD	BW	UGA	GA	Score	G	P	Mage	Srsp	Resus	HMD
1	F	N	Y	N	N	916	Y	30	Y	5	1	27	1	2	2
2	F	Y	N	N	N	855	N	26	N	4	0	29	1	2	2
3	M	Y	N	N	N	1000	N	30	N	3	2	31	15	5	2
4	F	N	Y	N	N	680	Y	32	Y	2	1	33	10	5	2
5	M	Y	N	N	N	570	N	22	N	2	1	23	0	8	2
6	F	N	N	Y	Y	970	Y	30.4	Y	8	0	30	1	5	2
7	M	N	N	Y	N	980	N	28	N	3	1	27	10	5	2
8	M	Y	N	N	N	1200	N	30	N	2	1	22	0	8	2
9	M	N	Y	N	N	955	Y	32	Y	3	1	24	5	5	2
10	M	Y	N	N	N	650	N	26	N	2	1	0	0	9	0
11	F	Y	N	N	N	480	Y	28	Y	1	1	18	10	5	2
12	M	Y	N	N	N	800	N	26	N	2	1	26	0	7	0
13	F	N	N	Y	Y	980	Y	31.2	Y	1	0	18	0	1	2
14	M	Y	N	N	N	1030	N	30.8	Y	0	0	32	30	7	2
15	F	Y	N	N	N	600	N	24	Y	2	1	25	0	5	2
16	M	Y	N	N	N	900	N	28	N	3	2	22	0	7	0
17	M	Y	N	N	N	1200	N	30	N	0	0	0	0	2	2
18	F	Y	N	N	N	1070	N	30	N	2	1	19	4	3	2
19	F	Y	N	N	N	700	N	24	N	2	1	24	0	1	0
20	F	Y	N	N	N	805	Y	28.8	Y	6	5	34	10	5	2
21	M	Y	N	N	N	850	Y	36	Y	2	0	26	5	5	3
22	M	Y	N	N	N	1150	N	28.2	Y	5	4	32	1	1	2
23	M	Y	N	N	N	760	N	24	N	2	1	38	1	3	2
24	M	Y	N	N	N	1060	N	30	N	0	0	37	1	3	2
25	M	Y	N	N	N	940	N	27	N	2	1	22	10	5	2
26	F	N	N	Y	Y	860	N	29.6	Y	3	2	31	1	3	3
27	M	Y	N	N	N	760	Y	35.2	Y	3	2	28	3	5	1
28	F	Y	N	N	N	580	N	23	N	4	3	30	0	8	0
29	M	N	Y	N	N	930	N	30	Y	2	1	30	5	5	2
30	F	Y	N	N	N	950	N	28	N	2	0	22	0	5	2
31	F	Y	N	N	N	680	N	25	N	2	1	28	1	3	2
32	F	Y	N	N	N	600	N	23	N	6	5	37	0	8	0
33	F	Y	N	N	N	400	N	23	Y	6	5	37	0	8	2
34	F	Y	N	N	N	900	Y	30	N	2	1	22	1	1	2
35	M	N	Y	N	N	750	Y	31.8	Y	2	1	26	6	5	6
36	M	N	Y	N	N	705	Y	27	Y	2	1	36	1	2	2
37	M	Y	N	N	N	755	Y	28	Y	2	1	37	0	3	2
38	F	Y	N	N	N	640	N	26	Y	4	3	36	0	8	2
39	F	Y	N	N	N	700	N	28	N	4	5	26	10	5	0
40	F	Y	N	N	N	630	N	27	Y	2	1	26	0	3	2
41	M	Y	N	N	N	1040	N	32	Y	4	3	32	10	5	2
42	F	Y	N	N	N	780	N	26	N	2	0	17	20	7	0
43	F	Y	N	N	N	810	N	28	Y	3	2	31	1	1	2
44	F	N	N	Y	Y	880	Y	28	Y	1	0	19	1	2	2
45	F	Y	N	N	N	840	N	28.4	Y	3	2	32	1	2	2
46	F	Y	N	N	N	835	Y	30	N	2	1	23	15	7	2
47	F	Y	N	N	N	400	Y	26	N	2	1	20	1	8	0
48	M	N	N	Y	Y	1130	Y	34.8	Y	3	2	35	1	2	3
49	F	Y	N	N	N	700	Y	28	Y	5	0	36	0	8	0
50	F	Y	N	N	N	920	N	30	Y	6	3	41	5	5	2
51	M	Y	N	N	N	750	N	24	N	3	0	22	0	8	0
52	F	Y	N	N	N	910	N	27	N	1	1	18	0	7	0

C No	M/F	ENND	LNND	PNND	D/CD	BW	UGA	GA	Score	G	P	Mage	Srsp	Resus	HMD
53	M	Y	N	N	N	770	N	25	N	4	0	27	0	5	0
54	M	Y	N	N	N	760	N	26	N	2	1	17	0	5	0
55	M	N	N	Y	N	1010	Y	31.5	Y	2	0	20	0	3	3
56	F	Y	N	N	N	980	N	30	N	4	1	35	1	1	2
57	M	Y	N	N	N	900	N	28	Y	2	1	23	0	5	0
58	F	Y	N	N	N	810	N	26	N	1	1	18	0	8	0
59	M	N	N	Y	Y	885	Y	29.4	Y	5	4	26	0	1	1
60	M	Y	N	N	N	650	N	24	N	0	0	0	0	8	0
61	F	N	N	Y	N	960	N	30.8	Y	1	0	20	0	1	2
62	F	Y	N	N	N	1120	N	28	N	2	1	24	0	5	2
63	M	N	N	Y	Y	1150	N	30	Y	1	0	24	7	6	2
64	F	Y	N	N	N	1160	N	30	N	1	1	17	1	1	6
65	M	Y	N	N	N	965	N	26	N	6	5	31	0	5	2
66	F	Y	N	N	N	510	Y	28	N	4	0	36	0	8	2
67	M	Y	N	N	N	750	Y	30	Y	2	1	34	1	1	2
68	M	N	N	Y	Y	1050	N	31.6	Y	1	0	23	1	1	2
69	F	Y	N	N	N	600	Y	30.5	Y	3	2	26	0	1	6
70	F	Y	N	N	N	1055	N	28	N	3	2	27	4	5	1
71	M	N	Y	N	N	1130	N	29.2	Y	3	0	27	15	7	2
72	M	Y	N	N	N	1100	N	25	N	4	3	35	15	5	0
73	F	Y	N	N	N	920	N	28	N	5	1	26	0	5	2
74	M	Y	N	N	N	950	N	26	N	1	1	21	0	5	6
75	F	N	Y	N	N	1010	N	30.8	Y	4	3	40	2	5	2
76	F	Y	N	N	N	865	N	27	N	2	1	20	9	5	2
77	M	Y	N	N	N	910	N	28	Y	2	1	26	0	5	0
78	M	Y	N	N	N	1180	N	31	Y	1	1	18	0	7	0
79	M	Y	N	N	N	940	Y	30	N	5	4	29	0	1	2
80	M	Y	N	N	N	860	N	28.4	Y	2	1	27	1	2	2
81	F	Y	N	N	N	900	N	26	N	4	2	26	5	5	2
82	M	N	N	Y	Y	1120	N	32.4	Y	1	0	21	1	2	2
83	M	Y	N	N	N	900	Y	34	Y	6	0	39	20	5	2
84	F	N	N	Y	N	790	Y	29.2	Y	5	0	26	1	2	2
85	F	Y	N	N	N	1000	N	28	N	1	1	22	5	5	2
86	F	Y	N	N	N	780	N	26	Y	3	2	25	0	8	0
87	M	Y	N	N	N	980	N	30	Y	8	6	29	0	2	2
88	M	Y	N	N	N	650	N	26	N	1	1	22	0	8	2
89	F	N	N	Y	Y	770	Y	32.4	Y	6	4	32	1	2	2
90	M	N	N	Y	N	1010	N	31.2	Y	1	0	26	12	7	2
91	F	Y	N	N	N	550	N	24	Y	2	1	30	0	8	0
92	M	Y	N	N	N	590	N	24	Y	3	2	24	1	8	0
93	M	Y	N	N	N	1245	N	30.8	Y	3	2	23	0	1	2
94	M	Y	N	N	N	800	N	24	N	0	0	37	0	8	0
95	F	Y	N	N	N	1195	N	30	N	1	1	24	0	7	0
96	M	Y	N	N	N	750	N	26	N	2	1	26	0	5	0
97	F	Y	N	N	N	600	N	21	N	2	1	23	0	5	5
98	M	Y	N	N	N	780	N	25	N	2	1	23	7	5	0
99	M	Y	N	N	N	750	N	25	N	3	2	24	0	8	2
100	M	Y	N	N	N	1050	N	30	Y	2	1	23	0	8	0
101	M	N	N	Y	Y	910	N	28	N	4	0	34	1	1	2
102	M	N	N	Y	N	950	Y	31.6	Y	2	1	21	1	2	2
103	M	Y	N	N	N	550	N	22	N	2	1	24	1	8	2

Appendix 4.IV : VLBW study: Deaths: Perinatal data

C No	Pnuem	PnThx	O2/V	D Vent	Apn	NEC	IVH	Dys D	Hrs D
1	0	0	2	0	0	1	1	0	7
2	0	0	5	0	0	0	0	0	1
3	0	1	4	2	1	1	6	0	2
4	0	1	4	9	1	1	4	0	9
5	0	0	5	0	0	0	0	2	0
6	2	1	4	12	1	1	3	0	81
7	5	1	4	9	4	1	6	0	99
8	0	0	5	0	0	0	0	2	0
9	5	1	4	23	1	1	1	0	27
10	0	0	6	0	0	0	0	3	0
11	0	1	5	0	0	1	2	48	0
12	0	0	6	0	0	0	0	1	0
13	0	1	2	0	1	1	1	0	44
14	0	1	4	2	1	1	1	0	4
15	0	0	5	0	0	0	0	2	0
16	0	0	6	0	0	0	0	1	0
17	0	2	4	1	1	0	2	23	0
18	0	1	4	3	3	1	6	0	4
19	0	0	5	0	0	0	0	4	0
20	0	3	4	0.5	1	1	0	15	0
21	0	0	2	0	0	3	2	0	4
22	3	0	4	3	0	1	0	0	3
23	0	1	5	0	1	1	2	0	3
24	0	1	4	1	1	1	1	0	2
25	0	2	4	0.3	0	0	0	6	0
26	0	1	2	0	2	1	1	0	99
27	0	1	2	0	1	3	2	0	6
28	0	0	6	0	0	0	0	1	0
29	0	1	4	11	1	1	1	0	12
30	0	1	4	3	4	1	4	0	4
31	0	0	5	0	0	0	0	5	0
32	0	0	5	0	0	0	0	4	0
33	0	0	5	0	0	0	6	6	0
34	0	2	4	0.5	1	1	2	36	0
35	0	1	4	5	1	1	3	0	12
36	0	1	4	5	4	1	5	0	18
37	0	1	5	0	2	1	5	0	7
38	0	0	5	0	0	0	0	5	0
39	0	0	5	0	0	0	0	1	0
40	0	1	5	0	1	0	0	0	1
41	0	2	4	5	1	1	2	0	5
42	0	0	5	0	0	0	0	12	0
43	0	1	5	0	1	0	2	0	1
44	0	1	2	0	3	1	8	0	99
45	0	1	5	0	1	1	0	0	4
46	1	1	4	2	1	0	0	0	2
47	0	0	5	0	0	0	0	4	0
48	0	1	2	0	1	1	2	0	99
49	0	0	5	0	0	0	0	0	1
50	0	1	5	0	0	0	2	0	2
51	0	0	5	0	0	0	0	17	0
52	0	0	6	0	0	0	0	1	0

C No	Pnuem	PnThx	O2/V	D Vent	Apn	NEC	IVH	Dys D	Hrs D
53	0	0	6	0	0	0	0	1	0
54	0	0	6	0	0	0	0	1	0
55	0	1	2	0	1	1	2	0	36
56	0	1	2	0	2	0	5	0	2
57	0	0	5	0	0	0	0	5	0
58	0	0	5	0	0	0	0	4	0
59	0	1	1	0	1	1	1	0	72
60	0	0	6	0	0	0	0	0	0
61	2	1	4	5	4	1	1	0	60
62	0	1	4	1	1	1	6	0	3
63	0	1	4	10	1	1	5	0	99
64	0	1	4	0	0	0	1	2	0
65	0	1	4	2	1	0	6	0	3
66	0	0	6	0	0	0	0	1	0
67	0	1	5	0	1	1	2	0	2
68	0	2	4	5	1	1	1	0	65
69	0	1	5	0	2	1	2	0	2
70	0	1	4	3	1	1	2	0	2
71	2	1	4	14	1	1	8	0	14
72	0	0	6	0	0	0	0	12	0
73	0	1	4	0.5	1	0	6	13	0
74	0	0	6	0	0	0	0	1	0
75	0	1	2	0	1	3	2	0	13
76	0	1	5	0	1	0	2	0	1
77	0	0	6	0	0	0	0	1	0
78	0	0	6	0	0	0	0	1	0
79	0	1	4	4	1	0	1	0	4
80	0	1	5	0	0	0	0	15	0
81	0	0	5	0	0	0	0	4	0
82	0	1	4	3	2	1	1	0	99
83	2	1	4	0.3	1	0	0	3	0
84	1	1	4	3	2	1	1	0	40
85	0	0	5	1	1	0	2	0	1
86	0	0	5	0	0	0	0	0	1
87	0	1	4	5	1	1	2	0	5
88	0	0	5	0	0	0	0	0	1
89	0	1	4	5	2	1	7	99	99
90	1	1	4	52	2	1	3	0	53
91	0	0	6	0	0	0	0	1	0
92	0	0	5	0	0	0	0	2	0
93	0	1	4	3	1	1	0	0	3
94	0	0	6	0	0	0	0	1	0
95	0	0	6	0	0	0	0	1	0
96	0	0	6	0	0	0	0	1	0
97	0	0	6	0	0	0	0	1	0
98	0	0	5	0	0	0	0	6	0
99	0	1	5	0	2	0	0	6	0
100	0	0	6	0	0	0	0	1	0
101	3	1	4	9	1	1	1	0	99
102	0	1	2	0	1	1	1	0	58
103	0	0	5	0	0	0	0	2	0

	Corrected scores						Uncorrected scores					
Cno	Loc	Pers/S	H/S	E/H	Perf	GQ	Loc	Pers/S	H/S	E/H	Perf	GQ
1	123	108	123	107	97	112	108	98	108	94	86	99
2	99	104	113	99	97	104	88	95	100	90	86	92
3	128	117	119	102	110	115	117	107	108	94	101	105
5	98.6	113	117.7	97	103.4	106	86	99	103	85	90	93
6	109	109	114	109	104	109	87	87	91	87	83	87
7	86	93	88	98	77	88	78	84	78	90	72	82
8	83	90	96	90	91	90	72	77	83	77	78	77
10	118	121	127	104	115	117	99	102	107	87	96	98
13	74	58	104	16	22	55	64	50	90	14	19	47
14	99	102	105	94	97	99.6	88	90	93	83	86	88
15	106.5	119	116	100	95.6	108	101	113	110	95	91	102
17	102	97	106	106	103	103	86	82	90	90	87	87
18	96	109	123	97	89	103	85	97	109	87	80	92
19	98	102	105	94	117	103	91	94	97	87	109	96
24	111	115	111	116	95	110	96	98	96	100	82	94
20	100	114	95	97	93	100	88	100	83	85	82	88
21	88	94	104	94	91	94	78	83	92	83	80	83
22	106	95	80	92	83	91	92	83	70	81	73	80
23	122	132	108	108	114	117	104	112	92	92	97	99
25	103	125	127	101	110	114	89	108	109	89	94	98
26	107	101	125	110	115	112	88	83	103	91	95	92
27	109	114	114	112	111	112	94	99	99	97	96	97
28	123	107	118	104	106	112	116	101	112	98	99	105
29	121	94	112	107	107	108	102	79	94	90	90	91
31	100	109	124	93	105	106	82	90	102	77	86	87
32	96	108	118	104	104	106	80	91	99	87	87	89
33	125	111	125	109	111	116	105	92	105	91	92	97
34	124	118	114	129	111	119	102	97	94	106	92	98
35	100.1	110	100	107	114	106	91	99	91	97	103	96
36	111	114	121	111	121	116	93	96	101	93	101	97
37	98	108	118	106	118	110	87	95	104	94	104	97
38	104	99	118	102	99	104	95	91	108	94	91	96
39	109	125	114	94	109	110	95	108	99	82	95	96
40	99	114	123	112	104	110	80	92	100	91	84	89
41	117	117	89	89	119	106	106	106	81	81	107	96
42	106	130	112	109	107	113	90	111	96	93	92	96
44	98	105	106	102	106	103	83	90	91	87	91	88
45	99	102	109	99	110	104	86	88	94	86	95	90
46	96	103	102	103	97	100	82	88	87	88	83	86
47	103	118	108	106	105	107	88	100	89	91	89	91
48	92	100	112	102	86	98	80	87	97	88	75	85
49	135	102	112	107	109	113	119	90	98	102	95	101
50	111	114	120	112	106	113	94	97	102	96	90	96
51	109	112	109	95	96	104	91	94	91	79	81	87
52	94	94	100	100	88	95	86	86	92	92	81	87
53	103	120	112	101	93	106	88	103	96	87	80	91
54	128	111	90	93	90	103	117	101	82	85	82	93
56	111	114	106	99	101	106	97	100	97	87	89	94

	Corrected scores						Uncorrected scores					
Cno	Loc	Pers/S	H/S	E/H	Perf	GQ	Loc	Pers/S	H/S	E/H	Perf	GQ
57	103	103	100	93	98	99	92	92	89	83	90	89
58	113	128	118	118	113	118.3	104	117	108	108	104	108
59	101	101	115	96	98	102	87	87	100	83	84	88
60	104	108	108	102	104	105	87	91	91	86	87	88
63	112	102	112	103	117	109	100	91	100	92	104	97
64	78	87	94	91	87	88	69	75	80	85	75	77
65	73	91	89	95	85	87	68	85	83	89	79	81
66	109	122	119	98	114	112	91	102	99	82	95	94
67	122	116	119	110	94	112	113	107	110	102	89	104
70	96	109	111	115	111	108	79	89	90	94	90	88
71	132	107	105	113	124	116	115	93	92	99	108	101
72	106	100	111	109	92	104	99	84	104	102	86	95
73	73	110	109	101	96	98	58	90	88	81	77	79
75	96	103	115	110	110	107	81	86	96	92	92	92
77	100	115	115	105	91	105	90	103	103	94	81	94
78	103	109	99	86	91	97	89	94	86	74	79	84
79	103	115	116	136	121	118	84	94	95	111	99	97
80	105	112	107	100	107	106	85	90	86	81	86	86
81	76	73	95	92	73	81	68	65	85	82	65	73
82	96	107	114	103	103	104	78	87	92	83	83	85
83	123	118	115	102	99	111	109	105	102	90	88	99
85	110	113	96	92	96	101	110	113	96	92	96	101
87	108	105	105	94	97	102	89	86	86	77	79	83
88	93	110	102	103	90	100	88	104	96	98	85	94
89	114	107	104	100	94	104	93	88	85	82	77	85
92	113	107	109	109	104	108	102	96	98	98	93	97
93	99	112	109	97	101	103.5	85	96	93	84	87	89
94	98	112	115	106	117	110	78	104	107	98	108	99
95	105	104	110	99	110	106	90	89	94	85	94	90
96	106	106	110	95	101	104	89	89	93	80	85	87
97	42	33	29	29	23	31	38	29	26	26	20	28
98	96	106	98	101	110	102	84	92	85	88	96	89
99	98	116	117	112	117	112	88	103	105	100	105	100
100	98	100	118	106	113	107	83	85	100	91	96	91
101	99	109	109	103	96	103	83	91	91	86	81	86
104	117	102	109	92	103	105	100	87	94	79	89	90
105	119	107	115	93	93	105	96	87	94	79	79	87
106	105	100	112	96	112	105	94	90	99	85	99	93
108	100	103	120	103	102	106	86	89	103	89	88	91
109	96	100	110	97	92	99	86	90	99	87	83	89
110	94	100	101	92	88	95	80	85	87	79	75	81
111	110	118	119	108	100	111	94	101	103	93	86	95
112	100	101	108	101	109	104	88	90	95	90	97	92
113	96	90	94	96	94	94	84	78	81	84	81	82
114	102	115	107	102	94	104	92	103	96	92	85	94
115	99	109	109	93	98	102	87	96	96	82	86	89
116	98	104	110	96	107	103	87	93	98	86	96	92
118	98	92	112	103	106	102	86	81	99	90	93	90

	Corrected scores						Uncorrected scores					
Cno	Loc	Pers/S	H/S	E/H	Perf	GQ	Loc	Pers/S	H/S	E/H	Perf	GQ
121	108	113	117	98	108	108	95	99	103	86	94	95
122	99	104	115	104	96	104	92	97	107	97	89	96
123	18	33	80	48	51	46	17	31	76	46	48	44
124	97	105	113	105	108	105	79	86	92	86	88	86
125	135	124	116	112	112	120	112	103	96	92	92	99
126	112	117	117	117	107	114	100	105	105	105	96	102
127	97	111	108	111	91	104	90	103	100	103	84	96
128	114	100	106	106	114	108	94	85	91	91	94	91
129	103	113	118	111	113	111	84	92	97	91	92	91
132	76	76	82	73	84	78	70	70	76	67	77	72

Appendix 4.VI: VLBW study: Griffiths scores (corrected and uncorrected) at two years of age.

	Corrected scores at 2 years of age							Uncorrected scores at 2 years of age						
C no	loc	Per/S	H/S	E/H	Perf	PR	GQ	Loc	Pers/S	H/S	E/H	Perf	PR	GQ
1	107	113	88	113	100	113	106	101	108	84	108	96	108	102
2	97	95	91	89	87	101	93	91	89	91	83	81	95	88
3	97	99	97	97	103	105	100	92	94	92	92	98	100	95
5	107	105	97	86	95	95	97	100	98	90	81	89	89	91
6	121	133	107	98	98	114	112	102	112	90	82	82	96	94
7	83	89	83	95	76	102	88	78	84	78	90	72	96	82
8	99	95	84	101	88	95	94	90	86	77	92	80	86	85
9	79	88	79	88	90	88	85	79	88	79	88	90	88	85
10	92	99	107	113	137	122	111	84	91	98	104	126	112	102
13	36	39	67	22	20	33	36	33	36	62	20	19	31	34
14	82	91	80	82	83	82	83	77	86	75	77	79	77	79
15	100	100	89	91	85	93	93	97	97	87	89	83	90	90
17	100	98	91	87	87	90	92	92	90	83	80	80	82	84
18	102	93	102	98	102	102	100	97	87	97	93	97	96	94
19	91	85	76	70	70	71	77	88	82	74	68	68	69	75
24	81	89	83	87	87	86	86	76	83	78	81	81	80	80
20	105	103	92	103	94	117	102	98	96	86	96	88	109	95
21	98	92	90	88	88	91	91	92	86	84	82	82	86	86
22	79	74	74	79	87	79	79	74	69	69	74	81	74	74
23	102	118	102	100	86	100	101	94	109	94	92	80	92	94
25	107	115	107	97	107	111	107	99	107	99	89	99	103	100
26	99	97	88	95	90	94	94	89	87	80	85	81	85	85
27	100	102	96	90	90	102	96	93	95	89	83	83	95	89
28	116	114	106	109	101	109	109	112	109	102	104	97	105	105
30	91	91	82	84	80	90	86	84	84	76	77	74	83	80
32	93	98	91	87	100	94	94	85	89	83	80	91	86	86
33	92	107	100	98	88	115	100	85	99	92	90	81	105	92
34	109	107	117	107	105	124	111	98	96	106	96	94	112	100
35	89	111	87	83	82	86	90	84	105	82	78	77	81	84
36	92	115	90	90	99	106	99	84	105	83	83	91	98	91
37	84	100	88	82	82	96	88	79	95	83	78	78	86	83
38	108	98	98	92	85	100	97	104	94	94	88	82	96	93
40	95	73	91	93	95	90	90	90	70	87	88	90	85	85
41	103	92	77	95	91	89	91	97	86	73	90	86	83	85
44	97	95	89	105	87	93	94	89	87	81	96	79	85	86
45	87	95	91	93	95	101	94	81	88	85	86	88	94	87
46	100	83	78	93	95	90	90	92	76	72	85	87	83	83
47	105	82	82	69	82	87	85	99	77	77	65	77	82	80
48	94	81	81	81	81	82	83	94	76	76	76	76	77	78
46	91	84	84	82	84	83	84	88	81	81	79	81	81	82
51	97	80	76	87	89	84	86	89	74	70	80	82	78	79
52	97	105	91	89	97	101	97	93	101	87	85	93	97	93
54	101	99	86	97	101	97	97	95	93	81	91	95	91	91
57	99	81	81	93	74	83	83	94	78	78	89	71	79	79
58	97	90	88	86	93	88	90	93	86	84	82	90	84	86
59	83	91	79	89	81	100	87	78	85	74	83	76	93	81
60	83	96	96	103	83	110	95	76	89	89	95	76	101	88
63	90	85	97	88	90	88	90	85	80	92	83	85	84	85
64	83	83	87	73	87	90	84	79	79	82	70	82	85	79
65	96	88	77	92	82	84	86	92	85	74	88	79	81	83
66	108	108	98	98	104	115	105	99	99	89	89	95	105	96
67	121	116	119	110	96	112	112	113	107	110	102	89	104	104
70	122	86	82	74	64	93	87	112	88	75	68	59	85	81
71	91	95	87	89	91	88	90	85	89	82	83	85	82	84

Appendix 4.VI: VLBW study: Griffiths scores (corrected and uncorrected) at two years of age. 136

	Corrected scores at 2 years of age							Uncorrected scores at 2 years of age						
C no	loc	Per/S	H/S	E/H	Perf	PR	GQ	Loc	Pers/S	H/S	E/H	Perf	PR	GQ
72	107	91	79	82	72	96	89	104	89	76	80	75	93	86
73	100	108	108	91	93	105	101	91	98	98	82	84	97	91
78	88	95	88	93	85	101	92	82	88	82	87	79	93	85
79	109	109	92	103	86	92	99	101	101	85	96	80	85	91
80	90	96	90	101	66	87	88	86	92	86	96	63	83	84
81	79	77	65	68	68	70	71	75	73	62	65	65	67	68
82	108	120	106	104	106	125	112	96	106	94	92	94	111	99
83	92	99	81	83	72	81	85	86	92	76	78	68	76	79
85	100	107	100	98	92	98	99	92	98	92	90	84	90	91
87	99	99	87	87	74	86	88	89	89	79	79	67	78	80
88	87	94	80	85	87	93	88	85	92	78	83	85	91	87
89	103	103	90	103	90	82	95	95	95	86	95	86	76	89
92	97	102	89	87	97	89	93	92	97	85	83	92	84	89
93	104	102	83	88	100	92	95	96	94	77	81	92	85	87
94	92	97	85	83	92	91	90	89	94	82	81	89	88	87
95	85	109	85	87	87	86	90	79	101	79	81	81	80	83
96	94	98	96	92	94	118	98	86	89	87	84	86	109	90
97	29	20	23	18	13	20	21	27	19	22	17	12	19	20
98	94	87	83	87	94	94	90	88	81	78	81	88	88	84
99	97	105	93	95	97	96	97	92	99	88	90	92	91	92
100	100	108	100	98	98	98	100	92	100	92	90	90	90	92
104	96	87	83	87	96	87	89	89	81	77	81	89	81	83
105	88	85	83	83	81	84	84	82	79	77	77	72	78	78
106	96	113	102	104	106	97	101	90	106	95	97	99	91	94
108	91	91	85	78	85	98	88	86	86	80	73	80	92	83
109	94	90	85	90	85	89	89	89	85	81	85	81	84	84
111	109	107	98	92	90	105	100	101	99	91	85	83	97	93
112	81	81	77	86	76	84	81	77	77	74	82	72	80	77
113	96	90	94	96	94	94	94	84	78	81	84	81	82	82
115	94	94	85	92	87	86	90	90	90	81	88	83	82	86
116	100	92	90	106	85	90	94	94	87	85	99	79	85	88
117	98	89	91	91	93	93	93	92	84	86	86	88	87	87
119	91	77	73	89	89	84	84	85	73	69	83	83	79	79
122	98	125	100	96	90	97	101	91	116	93	84	83	90	93
124	25	37	69	45	50	48	46	24	36	66	42	48	46	44
125	98	93	95	93	89	94	94	87	84	86	84	80	84	84
126	99	114	99	99	91	97	100	90	103	90	90	82	88	90
127	83	83	81	86	74	80	81	79	79	77	82	71	76	77
128	96	76	73	81	66	80	78	93	74	71	79	63	77	76
129	83	83	81	94	98	98	89	77	77	76	88	91	91	83
130	88	88	82	87	82	81	85	84	84	77	82	77	77	80
133	77	91	75	83	81	76	81	73	87	71	79	78	73	77

Appendix 4.VII : VLBW study, index children: Griffiths scores and anthropometric data at six years of age.

								Griffiths scores							
C No	Age	BW	GA	W	Ht	HC	M/F	Loc	Pers/S	H/S	E/H	Perf	PR	DQ	ADH
1	71.94	1050	33.2	18.5	110	49.0	F	99	94	78	97	83	78	89	N
2	67.87	1240	33.0	15.0	102	50.0	F	118	124	100	97	115	100	109	N
3	66.82	1190	35.0	17.0	106	50.0	F	127	103	97	94	97	88	101	Y
5	68.73	1170	32.4	16.0	111	48.0	M	109	103	79	77	74	77	87	Y
6	70.24	720	26.8	17.0	113	49.0	M	114	103	77	74	60	91	87	Y
7	80.03	1245	31.4	18.0	114	50.0	M	109	104	76	81	94	94	93	N
8	64.06	1240	30.0	16.0	107	53.0	M	100	94	72	75	72	75	81	Y
9	70.93	1225	40.0	11.0	103	44.5	F	99	87	85	85	82	64	84	Y
10	84.50	940	30.0	.	.	.	F	107	107	107	99	102	95	103	.
14	70.40	1090	33.2	15.0	107	50.0	F	108	97	77	102	88	79	92	N
15	65.08	1025	37.2	16.0	110	48.0	F	101	89	80	80	74	80	84	N
17	70.93	880	30.0	16.5	109	48.0	F	113	99	90	93	82	93	95	N
18	68.46	1145	33.6	19.0	107	51.5	M	94	94	100	94	100	74	93	N
19	69.58	1070	35.8	16.5	110	48.0	F	106	91	69	94	91	80	89	N
21	71.52	1160	32.8	15.0	121	50.0	F	115	82	70	65	65	73	78	N
22	74.51	1200	32.0	16.0	110	49.5	F	109	88	72	80	67	77	82	N
23	69.88	1010	30.8	17.0	110	48.0	F	97	120	91	91	86	74	93	Y
24	89.00	1165	31.6	.	.	.	M	99	94	79	90	79	103	91	.
25	66.98	870	31.4	15.0	106	48.0	F	125	96	99	93	75	86	96	N
27	75.62	1060	32.0	15.1	107	49.0	F	109	98	93	111	85	114	102	N
28	91.00	900	36.8	.	.	.	F	92	101	103	96	86	99	96	.
30	70.27	1200	30.0	17.0	100	50.0	M	100	94	80	86	94	74	88	N
32	65.41	860	30.0	15.0	109	50.5	F	98	119	76	92	76	85	91	N
33	63.57	990	30.0	17.0	118	49.0	M	110	101	88	101	104	104	101	N
34	74.01	1050	29.0	18.5	112	52.0	M	114	108	92	114	105	100	106	N
35	77.23	980	32.4	16.0	108	49.0	M	112	96	81	99	86	75	92	N
36	64.85	1095	30.0	19.0	107	50.0	F	126	123	92	86	80	120	105	N
37	74.67	880	33.0	16.0	109	50.5	F	108	95	100	105	95	89	99	N
38	83.00	1245	35.2	.	.	.	M	92	87	75	80	70	80	81	.
40	71.19	1200	34.0	18.0	110	50.0	M	118	104	73	76	79	85	89	Y
41	83.11	1190	33.0	.	112	52.0	M	108	89	72	75	70	53	78	.
47	74.67	940	31.0	18.0	112	50.0	F	105	97	64	89	75	86	86	Y
51	77.73	930	30.0	18.5	111	51.0	M	108	82	77	74	82	67	82	N
52	86.00	1140	35.2	.	.	.	F	105	88	81	100	84	79	90	.
54	61.83	1000	33.6	16.0	116	.	M	119	92	87	87	87	84	94	N
57	72.31	1125	33.6	20.0	113	51.5	F	94	97	83	86	78	81	87	N
58	70.40	1245	35.2	18.0	123	.	M	120	86	91	91	100	74	94	N
59	77.14	1115	32.0	19.0	128	52.0	F	109	94	81	91	75	70	87	N
63	75.66	900	33.2	16.5	.	.	F	120	109	93	83	104	85	99	N
65	67.61	1220	36.0	11.0	91	49.0	M	89	128	87	69	66	93	89	Y
66	65.57	1050	30.0	18.0	113	51.0	F	125	98	92	82	92	92	97	N
67	78.42	1245	34.0	24.0	120	.	M	100	77	87	100	77	64	84	.
70	74.21	780	28.0	16.5	108	49.0	M	112	96	88	80	69	67	85	N
72	68.07	850	36.4	17.0	110	50.0	M	106	97	85	91	79	79	90	N
73	77.66	915	28.0	21.5	120	50.0	F	110	100	90	92	87	95	96	.
78	83.50	1180	30.0	.	.	.	F	105	89	91	96	86	89	93	.
79	82.59	1100	28.0	22.5	120	54.5	F	116	104	101	102	82	108	102	.
80	81.44	1150	34.0	23.0	122	51.0	F	110	110	101	103	54	86	94	.

Appendix 4.VII : VLBW study, index children: Griffiths scores and anthropometric data at six years of age.

								Griffiths scores							
C No	Age	BW	GA	W	Ht	HC	M/F	Loc	Pers/S	H/S	E/H	Perf	PR	DQ	ADH
82	72.77	910	28.0	18.0	114	50.0	M	107	85	90	101	82	82	91	N
83	72.77	885	34.0	15.0	107	47.0	F	107	101	79	82	93	77	90	N
87	86.37	1120	28.4	22.0	118	51.5	M	114	96	94	103	71	85	94	.
88	70.34	1160	37.0	15.0	105	49.0	M	111	89	102	94	80	86	94	N
89	86.79	840	28.0	22.5	120	51.5	F	106	97	92	97	92	92	96	.
92	64.22	1010	34.2	20.0	112	51.0	M	125	88	81	78	88	84	91	N
93	77.50	1120	31.6	.	.	.	F	78	73	62	49	55	70	65	.
98	84.00	1180	32.0	19.5	117	52.5	M	105	109	102	100	95	93	101	.
99	78.61	1150	33.6	21.0	124	50.0	F	109	117	99	107	69	117	103	.
100	71.68	900	31.0	17.0	110	51.0	M	110	104	113	104	93	107	105	N
104	67.87	1090	28.0	18.0	113	51.0	M	106	103	94	118	76	79	96	N
105	67.87	1100	31.0	18.0	113	51.0	M	115	118	91	103	94	82	101	N
106	78.68	1175	32.4	17.0	114	50.5	F	104	99	81	99	96	86	94	N
108	71.09	1050	31.6	18.5	109	49.0	F	110	104	87	93	85	73	92	N
109	69.09	1230	34.0	15.0	104	50.0	F	72	78	.	90	82	58	76	N
111	63.76	900	31.6	19.5	113	50.0	M	109	113	91	84	94	78	95	N
112	74.97	1145	33.2	21.0	111	50.0	M	99	115	88	67	69	83	87	N
113	77.86	700	26.8	19.5	119	47.0	M	104	94	86	91	86	86	91	N
114	73.36	960	34.0	18.5	109	51.0	F	110	104	90	101	90	85	98	N
115	85.87	1140	32.8	.	.	.	M	100	95	93	95	77	102	94	.
116	64.03	930	33.6	14.5	105	51.0	M	106	97	84	91	84	75	90	N
118	71.55	1210	32.8	19.5	117	50.5	M	104	99	73	93	76	66	85	N
121	68.40	1010	32.0	16.5	110	49.5	M	118	100	88	79	97	100	97	N
124	71.45	1240	28.0	17.0	108	52.0	M	123	109	103	87	109	98	105	N
125	69.25	880	29.0	16.0	111	49.5	F	116	101	78	90	90	75	92	N
126	67.81	800	34.0	16.0	117	.	F	124	126	0	79	74	71	95	N
128	76.91	1170	31.6	21.0	117	52.0	M	122	104	91	96	91	81	98	Y

On H/S subscale "." indicates child refused to co-operate. DQ calculated from 5 sub-scales.

Appendix 4.VIII : VIbw study, control children: Griffiths scores and anthropometric data at six years of age

							Griffiths scores							
C No	Age	BW	W	Ht	HC	M/F	Loc	Pers/S	H/S	E/H	Perf	PR	DQ	ADH
1	72.57	2990	22.0	119	51.0	F	125	125	75	114	108	100	108	N
2	70.43	3000	18.5	113	49.0	F	106	106	94	89	100	91	98	N
3	63.30	4200	23.0	116	52.0	F	127	127	102	108	127	95	114	N
4	70.99	2800	17.5	109	49.0	M	107	99	93	90	82	96	95	N
5	75.99	3000	20.5	119	50.5	M	109	112	91	99	88	99	100	N
6	66.89	2950	18.5	113	50.0	M	122	93	90	87	93	84	95	N
7	60.74	3700	17.5	107	53.0	M	115	105	89	121	121	82	106	N
8	62.02	3000	18.0	106	50.0	F	123	84	100	81	94	90	95	N
9	68.96	2960	18.5	109	50.0	F	110	99	93	90	78	75	91	N
10	66.62	2570	16.0	101	49.0	F	131	120	81	93	75	87	98	N
11	63.99	3360	19.0	112	51.0	F	119	103	88	100	100	84	99	N
12	73.62	4400	23.0	132	50.0	F	101	112	98	98	95	93	100	N
13	70.14	3750	21.0	115	51.0	F	114	86	66	83	71	86	84	Y
14	73.29	3000	18.0	113	52.5	F	112	99	85	99	82	79	93	N
15	75.46	3000	27.0	132	53.0	F	115	104	91	107	93	96	101	N
16	65.87	3000	15.0	101	48.5	F	118	88	76	103	88	91	94	N
17	73.00	3300	25.0	128	.	M	112	110	99	110	99	96	104	N
18	74.44	3000	19.0	108	51.0	F	114	108	89	108	108	100	105	N
19	66.95	3000	19.0	109	53.0	M	122	84	93	96	105	93	99	N
20	67.81	2676	15.5	113	49.5	F	100	103	91	88	76	76	89	N
21	62.42	3500	17.0	113	50.0	M	134	109	99	99	96	91	105	N
22	73.92	3000	20.5	116	51.0	M	116	108	89	95	97	105	102	N
23	77.43	3500	.	.	.	M	112	91	109	86	114	96	101	N
24	65.97	3200	19.0	109	51.0	F	115	112	85	91	88	88	97	N
25	72.50	3000	18.0	109	51.0	F	112	118	107	90	118	99	107	N
26	65.34	3000	17.0	106	52.0	M	108	95	98	108	95	89	99	N
27	75.03	3000	17.0	.	.	F	101	104	72	67	67	72	81	N
28	74.21	2880	17.0	109	49.5	F	130	103	84	84	78	95	96	N
29	70.14	3000	18.0	116	51.0	M	134	111	106	111	86	111	110	N
30	57.16	3290	16.0	107	.	M	140	102	88	84	88	98	100	N
31	74.08	3000	18.0	111	51.0	F	116	103	89	111	121	116	109	N
32	75.82	2900	19.0	111	52.5	F	121	97	84	95	92	87	96	N
33	61.24	3480	15.0	111	.	M	108	121	98	89	89	92	100	N
34	71.45	3000	26.0	121	49.0	F	103	115	95	106	101	112	105	N
35	69.68	2550	16.5	107	50.5	M	113	113	81	72	78	90	91	N
36	72.93	3500	22.5	114	52.0	F	110	110	94	99	99	79	99	N
37	77.04	3250	.	.	.	M	112	99	81	104	91	88	96	N
38	62.75	3000	18.0	114	51.0	M	116	113	100	87	90	81	98	N
39	72.80	2940	19.0	111	50.0	M	101	90	82	85	79	77	86	Y
40	72.04	3500	22.0	120	51.5	M	114	117	94	94	114	93	106	N
41	74.05	3500	.	.	.	M	111	89	103	100	96	111	102	N
42	69.48	3790	20.0	123	52.0	M	109	118	112	112	129	92	113	N
43	69.02	2910	19.0	116	50.0	M	104	122	90	113	116	90	106	N
44	74.38	3220	17.5	113	51.0	F	111	100	95	100	81	87	96	N
45	70.04	3000	18.5	107	49.0	F	140	114	97	89	71	109	103	N
46	73.06	3400	18.5	109	50.5	M	118	121	85	74	77	74	92	N
47	71.09	3000	21.5	114	50.0	F	115	104	73	68	82	93	89	N
48	68.20	3000	21.0	115	50.5	M	121	129	100	97	106	97	108	N
49	76.71	3000	17.5	114	51.0	M	105	100	95	105	108	92	101	N
50	74.61	3000	20.0	111	50.0	F	107	121	91	102	97	99	103	N

Appendix 4.VIII : Vlbw study, control children: Griffiths scores and anthropometric data at six years of age

							Griffiths scores							
C No	Age	BW	W	Ht	HC	M/F	Loc	Pers/S	H/S	E/H	Perf	PR	DQ	ADH
51	62.32	3000	19.0	108	51.5	M	123	110	123	126	116	103	117	N
52	75.95	3000	17.0	116	51.0	M	116	116	76	92	103	105	101	N
53	72.24	2750	.	.	.	M	124	97	117	100	83	114	106	N
54	70.34	3100	18.0	107	50.0	M	126	100	83	100	91	83	97	N
55	67.74	4060	21.0	110	50.5	F	113	116	107	77	65	86	94	N
56	68.99	2990	20.0	118	51.0	F	136	113	96	93	102	119	110	N
57	73.03	3520	21.0	117	52.0	M	112	104	93	112	93	90	101	N
58	60.91	3000	18.0	107	51.0	M	131	121	89	92	118	111	110	N
59	83.51	2800	20.0	125		M	106	82	82	92	77	68	84	.
60	82.88	3000	.	.	.	F	111	101	84	101	92	99	98	.
61	84.13	3100	17.5	105	52.0	M	105	83	79	83	76	81	85	.
62	86.79	3000	22.0	120	54.0	F	108	94	92	99	69	97	93	.
63	84.00	3300	22.5	123	51.0	F	107	100	64	81	50	76	80	.
64	83.54	2950	26.5	124	54.0	F	113	96	65	86	60	93	86	..
65	84.00	3000	.	.	..	M	105	95	83	91	76	98	91	.
66	90.00	3200	.	.	.	F	102	96	67	87	89	93	89	.
67	87.50	2750	.	.	.	M	96	101	80	96	107	98	96	.
68	86.50	3000	.	.	.	F	111	113	111	102	93	111	107	.
69	90.00	3200	.	.	.	M	102	98	93	89	102	96	97	..
70	80.00	3000	.	.	.	F	120	103	80	88	75	93	93	.

Appendix 5.I: Qestionnaire for HIE study

NAME: _____

ADDRESS: _____

Telephone: ########

Contact person: _____

Folnumber: ##########

Mat age: ##

Gravidity: ##

Parity: ####

Delivery: ##
1 NVD
2 BREECH
3 FORCEPS
4 VACUUM
5 C/S Vertex
6 C/S BR
7 C/S FAILED 3 or 4

Birthdate: <dd/mm/yy>

Place of delivery: ##
1 GSH
2 MMH
3 KMOU
4 GMOU
5 RMOU
6 HPMOU
7 HVMOU
8 HOME/BBA
9 PRIVATE

WEIGHT: ####

SEX: #
1 MALE
2 FEMALE

HEAD CIRC: ##.#

APGAR SCORE 1 min #

5 min #

10 min #

CORD pH: #.##

CORD BE: ##.##

HIE Maximum score: ##

Became normal: <Y>

Normal score day: ##

Days ventilated: ###

Days oxygen: ###

Anticonvulsant: <Y>

No days: ##

Antibiotic: <Y>

No days: ##

Magnesium: <Y>

No days: ##

Dexamethasone: <Y>

No days: ##

Mannitol: <Y>

No days: ##

Number u/s done: #

Cerebral ultrasound: #

1 NORMAL
2 OEDEMA
3 SUBCORTLEUC
4 I/CHX
5 HYDROCEPH

CONVULSIONS: <y>

Died: <Y>

DISCHARGE DATE: <dd/mm/yy>

18 weeks: #

1 NORMAL
2 CP
3 CP/MR
4 HYPOTONIA
5 SUSPECTMR
6 LOST
7 DIED
8 SUSPECTDEV
9 DIEDCP

18 weeks comment:_____

1 year: #

1 NORMAL
2 CP
3 CP/MR
4 MR
5 MOTORDELAY
6 LOST
7 DIED

1 year comment:_____

Griff A: ###

Griff B: ###

Griff C: ###

Griff D: ###

Griff E: ###

GQ: ###

Normday7: <Y>

scoreday3: ##

day1: ##

day2: ##

day3: ##

day4: ##

day5: ##

day6: ##

day7: ##

day8: ##

day9: ##

day10: ##

3YDate: <dd/mm/yy>

3Yage: ##.#

Control: <Y>

3Yheight: ###.#

3Yweight: ##.#

3YHC: ##.#

Seizures: <Y>

Medication: <Y>

3 years: #

1 NORMAL
2 CP
3 CP/MR
4 MR
5 MOTOR
6 LOST
7 DIED

3Y comment:_____

Griff3L: ###

Griff3PS: ###

Griff3HS: ###

Griff3EH: ###

Griff3P: ###

Griff3PR: ###

Griff3GQ: ###

Appendix 5.II: HIE cohort: Perinatal and outcome data including Griffiths scores

Perinatal data																		Griffiths scores					
C	N	M/F	Max	S	Norma	D	vent	D 1	D 2	D 3	D 4	D 5	D 6	D 7	D 8	D 9	D 10	NA	CP	Loc	Per/S	H/S	E/H	Perf	GQ
1	2	4	N	7	0	3	1	4	1	1	0	0	0	0	0	0	1	N	114	121	138	129	124	125
2	1	2	N	4	0	1	2	1	0	0	0	0	0	0	0	0	1	N	134	104	115	104	104	111
3	2	15	N	7	2	15	14	8	7	7	4	0	0	0	0	1	N	112	92	105	105	112	105
4	1	16	Y	0	0	16	15	14	12	10	7	7	7	8	8	3	Y	10	19	6	0	3	8
5	2	14	Y	12	0	2	5	14	14	12	12	8	9	2	2	3	Y	33	29	33	0	29	25
6	1	10	Y	7	0	6	8	10	4	5	1	0	0	0	0	1	N	157	122	128	109	115	126
7	1	10	N	4	0	10	4	2	0	0	0	0	0	0	0	1	N	128	121	106	128	109	119
8	1	17	Y	11	5	5	17	15	17	15	15	15	13	10	6	1	N	135	117	115	115	98	115
9	1	5	N	2	0	5	0	0	0	0	0	0	0	0	0	8	N	121	123	130	121	117	122
10	2	15	Y	0	0	7	15	13	15	11	11	9	9	10	9	2	Y	24	32	45	32	24	31
11	1	18	Y	9	2	3	8	11	16	18	9	6	4	0	0	2	Y	23	53	57	17	13	33
12	2	7	N	7	0	7	7	5	3	1	1	0	0	0	0	1	N	102	81	99	96	93	94
13	2	18	Y	12	7	0	11	18	17	16	16	10	6	4	1	5	Y	82	103	112	118	93	101
14	1	3	Y	6	0	0	2	3	2	1	0	0	0	0	0	1	N	131	118	126	107	121	120
15	1	12	Y	9	0	0	2	11	12	12	12	10	6	0	0	1	N	120	119	120	120	109	118
16	1	12	Y	12	0	7	9	12	10	10	10	7	10	10	9	9	Y	.	.	.	.	.	.
17	1	8	N	0	0	1	3	3	5	8	5	5	0	0	0	1	N	113	124	117	111	96	113
18	1	5	N	5	0	5	3	2	2	0	0	0	0	0	0	6	N	124	105	96	109	126	111
19	1	1	N	2	0	1	0	0	0	0	0	0	0	0	0	1	N	108	104	100	108	108	106
20	1	19	N	0	10	16	19	19	19	17	17	16	15	13	8	2	Y	15	21	34	6	0	15
21	1	14	Y	10	0	2	7	14	12	12	11	8	2	1	0	1	N	119	117	119	107	106	113
22	2	13	N	6	4	0	13	11	5	3	3	0	0	0	0	6	N	138	112	138	112	112	122
23	1	5	N	2	0	5	0	0	0	0	0	0	0	0	0	1	N	130	127	116	111	111	118
24	2	10	Y	0	0	10	4	4	8	9	5	4	0	0	0	1	N	120	118	139	134	116	125
25	2	16	Y	0	3	10	16	14	14	11	11	10	9	9	9	5	Y	57	46	60	29	21	43
26	2	17	Y	10	4	3	16	17	15	14	12	13	4	2	4	5	Y	70	109	71	100	93	89
27	1	19	Y	0	5	14	16	18	17	19	18	18	14	14	12	9	Y	.	.	.	.	.	.
28	1	19	Y	0	5	18	14	20	20	19	0	9	0	0	0	9	Y	.	.	.	.	.	.
29	1	14	Y	13	0	2	10	14	12	10	9	7	7	4	3	8	N	114	110	105	100	105	107
30	1	17	Y	0	3	9	17	16	16	16	16	15	14	14	14	2	Y	.	.	.	.	.	.
31	1	19	Y	0	0	11	19	18	16	14	15	11	9	9	7	2	Y	16	10	6	4	0	7
32	1	13	Y	8	0	0	0	13	6	6	2	1	0	0	0	1	N	98	128	127	105	104	112
33	1	10	Y	5	0	7	10	6	5	0	0	0	0	0	0	1	N	144	119	135	118	126	128
34	2	12	Y	14	0	1	1	0	2	6	11	12	10	4	4	1	N	148	116	119	124	124	126
35	1	16	Y	12	4	14	16	15	16	12	11	8	8	6	6	3	Y	13	26	36	33	16	25
36	2	15	Y	30	3	8	9	15	13	12	8	11	8	9	5	4	Y	78	98	106	89	82	91
37	1	17	Y	0	6	10	15	17	17	15	15	14	10	10	9	9	Y	.	.	.	.	.	.
38	2	10	Y	0	0	5	10	10	7	1	1	0	0	0	0	1	N	103	110	104	104	103	105
39	1	15	Y	0	1	15	11	9	11	11	9	9	6	4	3	1	N	114	121	129	110	124	120
40	1	12	Y	0	0	0	0	5	12	10	10	7	5	5	3	2	Y	77	100	92	95	95	92

Appendix 6.I: Questionnaire for Neurodevelopmental evaluation study

NAME: _____

ADDRESS: _____

Soc code: ####

Telephone: ########

Contact person: _____

Number: ########

CaseID: ###

Birthdate: <dd/mm/yy>

WEIGHT: ####

SEX: # 1 MALE
2 FEMALE

HEAD CIRC: ##.#

Gestation: ##.#

SGA 10th: <Y>

SGA 3rd: <Y>

APGAR SCORE 1 min #

5 min #

CORD pH: #.##

CORD BE: ##.##

Days ventilated: ###

Days oxygen: ###

BPD: <y>

APNOEA: # 1 NO
2 YES
3 CPAP
4 IPPV

NEC: # 1 NO
2 YES
3 SURGERY

Cerebral ultrasound: # 1 NORMAL
2 I
3 II
4 III
5 SHUNT
6 IV
7 PVL
8 SUBCORT
9 NILDONE

CONVULSIONS: <y>

CNS abnormality: <y>

Syndrome: <y>

HYPOGLYCAEMIA: <y>

Symptoms: # 1 JITTERY
2 CONVULSIONS
3 SHOCK

DISCHARGE DATE: <dd/mm/yy>

Dubowitz: #	1 NORMAL
	2 1
	3 2-3
	4 4+
Risk Rating: #	1 1000-1499G,RDS,AN,HY
	2 750-999G,IVH1OR2,BPD
	3 <750,IVH3OR4,PVL,FIT
	4 SYNDROMES
18 weeks: #	1 NORMAL
	2 DEVDELAY
	3 ASYMMETRY
	4 TRANSDYSTONIA
	5 DEVRETARDED
	6 CP
	7 DIED
	8 LOST
1 year: #	1 NORMAL
	2 DEVDELAY
	3 DYSTONIA
	4 CP
	5 DIED
	6 LOST
	7 NORMALCHW
	8 SUSPECTCHW
	9 NORMALNOTSEEN
	10 SUSPECTNOTSEEN

Griff A: ###

Griff B: ###

Griff C: ###

Griff D: ###

Griff E: ###

GQ: ###

Griff chronA: ###

Griff chronB: ###

Griff chronC: ###

Griff chronD: ###

Griff chronE: ###

ChronGQ: ###

Appendix 6.II : Neurodevelopmental assessment study: Perinatal data and one year outcome with corrected and uncorrected Griffiths GQ

Perinatal data																	Outcome					
C No	BW	M/F	GA1	mir5	mirpl	BE	D vent	BPD	Apn	NEC	U/S	S	CNS	Sx	Hypo	Dub	PRR	INA	1 Yr	GQc	GQu
1	1100	1	32	2	9	7	11	2	N	2	1	3	N	N	N	N	3	2	3	1	101	88
2	1120	2	33	7	9	7	12	0	N	1	1	3	N	N	N	N	1	2	1	7	.	.
3	1220	2	31	8	9	.	.	0	N	1	1	1	Y	N	N	N	1	1	1	1	102	88
4	1300	2	33	6	8	0	0	0	N	1	1	9	N	N	N	N	1	1	1	7	.	.
5	1690	2	34	4	8	7	18	0	N	1	1	9	N	N	N	N	1	1	1	1	133	118
6	715	1	26	2	9	0	0	0	N	2	2	1	N	N	N	N	1	3	1	1	126	100
7	950	1	34	1	4	7	15	0	N	1	1	1	N	N	N	N	1	2	1	1	107	97
8	940	1	31	5	9	7	6	0	N	1	1	1	N	N	N	N	1	2	1	1	119	100
9	1290	1	32	7	9	0	0	0	N	1	1	1	N	N	N	N	1	1	1	1	112	96
10	995	2	36	5	8	0	0	0	N	1	1	1	N	N	N	N	2	2	1	1	106	98
11	900	1	31	9	9	0	0	5	N	4	1	7	N	N	N	N	1	2	1	1	112	95
12	1200	1	31	9	9	0	0	0	N	1	1	1	N	N	N	N	2	3	1	1	112	94
13	1145	2	31	4	7	7	7	0	N	1	1	1	N	N	N	N	1	1	1	1	117	100
14	1350	2	33	1	6	7	24	1	N	1	1	1	N	N	N	N	1	2	1	1	102	90
15	625	2	31	2	8	7	11	0	N	1	1	1	N	N	N	N	2	3	2	1	108	93
16	880	1	28	5	5	0	0	0	Y	1	1	3	N	N	N	N	1	2	1	1	102	86
17	2260	1	40	8	9	0	0	0	N	1	1	1	Y	N	N	N	1	3	1	1	116	116
18	2750	2	39	2	6	7	12	0	N	1	1	1	N	N	N	N	1	1	2	1	109	107
19	2550	2	40	9	9	0	0	0	N	1	1	1	Y	Y	Y	N	4	4	6	4	37	37
20	1090	2	31	9	9	0	0	0	N	1	1	2	N	N	N	N	1	2	1	1	120	102
21	950	2	30	9	9	0	0	0	N	1	1	2	N	N	N	N	1	2	1	1	112	96
22	1120	2	29	9	9	7	5	0	N	1	1	1	N	N	N	N	1	2	6	4	142	112
23	1020	1	32	9	9	7	1	21	Y	4	1	1	N	N	N	N	2	2	2	1	105	91
24	900	2	29	8	8	0	0	0	N	1	1	1	N	N	N	N	2	2	1	1	117	97
25	1000	2	29	7	9	0	0	0	N	1	1	3	N	N	N	N	1	2	1	1	117	97
26	3315	1	38	4	5	7	10	0	N	1	1	1	N	N	N	N	1	1	1	1	114	111
27	1250	2	33	7	9	7	7	0	N	1	1	1	N	N	N	N	1	1	1	1	107	94
28	890	2	33	9	9	7	8	0	N	1	1	1	N	N	N	N	1	2	1	7	.	.
29	1750	1	35	6	7	0	0	0	N	2	1	3	N	N	N	N	1	2	2	1	106	97
30	1190	1	33	9	9	7	7	0	N	1	1	3	N	N	N	N	1	2	1	1	122	110
31	1270	2	33	7	9	7	3	1	N	1	1	1	N	N	N	N	2	1	1	1	125	109
32	840	2	32	8	9	7	2	0	N	1	1	1	N	N	N	N	1	2	1	1	123	108
33	1160	2	34	3	6	7	8	0	N	1	1	1	N	N	N	N	1	1	3	1	106	95
34	910	1	34	6	9	7	8	5	N	1	1	1	N	N	N	N	1	2	1	1	120	105
35	820	2	32	0	0	0	0	0	N	1	2	3	N	N	N	N	1	2	5	1	92	81
36	1400	1	37	8	9	7	7	0	N	1	1	1	N	N	N	N	1	1	4	1	112	105
37	1390	1	32	7	9	7	4	0	N	1	1	1	N	N	N	N	1	1	1	1	114	97
38	1300	1	30	8	9	7	5	0	N	1	1	1	N	N	N	N	2	1	1	1	119	99
39	1240	2	35	4	7	0	0	0	N	1	1	7	N	N	N	N	1	1	2	7	.	.
40	2250	2	42	3	8	7	13	2	N	1	1	1	Y	N	N	Y	4	3	1	4	75	75
41	845	2	31	8	8	7	7	4	N	1	1	3	N	N	N	N	3	2	1	1	109	94
42	1470	1	30	9	9	0	0	0	N	1	2	1	N	N	N	N	1	1	1	1	125	106
43	3150	1	40	8	9	0	0	0	N	1	1	1	Y	N	N	N	4	3	4	1	94	94
44	3100	1	40	3	6	0	0	0	N	1	1	1	Y	N	N	N	1	3	2	1	107	107
45	1360	1	33	6	8	7	15	0	N	1	1	5	N	Y	N	N	4	4	6	5	.	.
46	810	2	30	7	8	7	14	0	N	2	1	1	N	N	N	N	1	2	1	1	112	96
47	800	2	31	4	7	0	0	0	N	2	1	9	N	N	N	N	1	2	2	1	101	87
48	2580	1	38	2	6	7	20	0	N	1	1	1	N	N	N	N	3	1	1	1	106	102

Appendix 6.II : Neurodevelopmental assessment study: Perinatal data and one year outcome with corrected and uncorrected Griffiths GQ

Perinatal data																		Outcome					
C No	BW	M/F	GA1	mir5	mirpl	BE	D	vent	BPD	Apn	NEC	U/S	S	CNS	Sx	Hypc	Dub	PRR	INA	1 Yr	GQc	GQu
49	1325	2	35	6	9	0	0	0	N	1	1	1	N	N	N	N	1	1	4	1	123	113
50	1700	2	34	3	6	7	14	0	N	1	1	1	N	N	N	N	1	1	1	7	.	.
51	1075	1	29	9	9	7	7	0	N	1	1	2	N	N	N	N	1	2	3	1	106	89
52	980	1	29	2	4	7	6	5	N	1	1	7	N	N	N	N	1	2	1	1	105	88
53	1250	1	36	6	9	7	6	0	N	1	1	9	N	N	N	N	1	1	1	1	116	108
54	1550	2	33	3	6	7	18	0	N	1	1	1	N	N	N	N	1	1	3	1	104	96
55	1075	1	37	9	9	7	2	0	N	1	1	1	N	N	N	N	1	1	2	1	110	103
56	1400	2	38	8	9	0	0	0	N	1	1	1	N	N	Y	N	3	4	5	5	.	.
57	1135	2	37	3	9	7	8	0	N	1	1	1	N	N	N	N	2	2	1	1	105	100
58	2400	1	41	3	4	7	14	0	N	1	1	1	N	N	N	N	1	1	2	1	115	115
59	1280	2	35	9	9	0	0	0	N	1	1	1	N	N	N	N	1	1	1	1	115	106
60	1200	2	36	3	9	0	0	0	N	1	1	1	N	N	N	N	1	2	1	2	102	95
61	1060	2	34	9	9	7	10	0	N	1	1	1	N	N	N	N	1	1	1	1	103	92
62	3580	2	41	1	3	0	0	5	N	1	1	1	Y	N	N	N	4	3	2	6	.	.
63	900	2	31	0	7	0	0	1	N	1	1	3	N	N	N	N	1	2	1	1	97	83
64	1660	1	34	3	4	7	7	6	N	1	1	1	N	N	N	N	1	1	2	1	111	101
65	3000	1	40	1	2	7	27	6	N	1	1	8	Y	Y	N	N	2	3	5	4	.	.
66	1970	1	33	4	4	7	7	1	N	1	1	9	N	N	N	N	1	1	1	1	90	86
67	2640	1	40	4	7	7	22	5	N	1	1	1	Y	N	N	N	4	3	1	1	109	109
68	3360	1	39	3	8	7	20	0	N	1	3	1	N	N	N	N	1	2	1	1	112	109
69	1180	2	36	8	8	0	0	0	N	1	1	1	N	N	N	N	1	1	1	1	122	112
70	1130	2	32	1	8	7	8	0	N	1	1	1	N	N	N	N	1	1	1	1	96	85
71	1340	1	34	6	9	0	0	0	N	1	1	1	N	N	N	N	2	1	1	1	97	89
72	2150	1	37	2	4	7	7	0	N	1	1	9	N	N	N	N	1	1	1	1	103	98
73	2780	2	40	1	7	7	25	0	N	1	1	9	N	N	N	N	2	2	1	9	.	.
74	1530	1	35	4	7	7	18	0	N	2	1	1	N	N	N	N	1	2	4	1	110	101
75	1300	2	32	0	0	0	0	0	N	1	1	9	N	N	N	N	1	1	1	5	.	.
76	975	2	30	1	5	7	16	3	N	1	1	3	N	N	N	N	1	2	4	1	106	93
77	1125	1	33	9	9	7	7	2	Y	1	1	1	N	N	N	N	2	1	3	1	116	103
78	1450	1	35	9	9	7	8	0	N	1	1	1	N	N	N	N	3	1	1	1	106	97
79	3400	2	40	1	6	0	0	1	N	1	1	1	N	N	N	N	1	1	3	1	105	105
80	1350	2	34	9	9	7	0	0	N	1	1	1	N	N	N	N	1	1	1	1	108	96
81	2600	1	39	9	9	0	0	2	N	1	1	1	N	N	N	N	3	1	5	8	63	63
82	1200	2	33	3	7	0	0	9	N	1	1	2	N	N	N	N	1	1	1	6	.	.
83	3160	1	40	2	4	7	27	1	N	1	1	1	Y	N	N	N	4	3	5	4	36	36
84	1100	1	33	8	9	7	4	0	N	1	1	4	N	N	N	N	1	2	1	6	.	.
85	1450	1	32	6	7	0	0	0	N	2	1	2	N	N	N	N	2	2	1	2	104	91
86	2500	2	40	2	7	7	1	0	N	1	1	1	N	N	N	N	1	1	1	1	101	101
87	1475	2	36	6	9	7	3	0	N	1	1	1	N	N	N	N	1	2	1	1	153	141
88	1045	2	34	6	8	7	3	0	N	1	1	1	N	N	N	N	1	1	1	1	109	99
89	1270	2	32	5	6	0	0	4	N	4	1	1	N	N	N	N	2	2	1	1	107	98
90	1350	1	34	5	5	0	0	0	N	2	2	7	N	N	N	N	3	3	1	1	105	94
91	1220	1	29	5	9	7	7	1	N	4	2	3	N	N	N	N	1	2	1	1	123	100
92	2400	1	39	1	2	7	7	4	N	1	1	1	N	N	N	N	1	1	3	1	107	105
93	990	1	33	6	5	0	0	0	N	1	1	1	N	N	N	N	1	2	1	1	131	114
94	1495	1	34	9	9	0	0	0	N	1	1	1	N	N	N	N	1	1	1	1	93	87
95	2120	1	38	2	7	7	11	4	N	1	1	8	N	N	N	N	4	3	6	5	.	.
96	1050	1	33	9	9	7	3	0	N	1	1	1	N	N	N	N	1	1	1	1	109	96

Appendix 6.II : Neurodevelopmental assessment study: Perinatal data and one year outcome with corrected and uncorrected Griffiths GQ

Perinatal data																	Outcome					
C No	BW	M/F	GA1	mlr5	mirpH	BE	D vent	BPD	Apn	NEC	U/S	S	CNS	Sx	Hypo	Dub	PRR	INA	1 Yr	GQc	GQu
97	1680	1	38	1	2	7	8	0	N	1	1	1	N	N	N	N	1	1	1	1	100	95
98	2080	1	34	1	3	0	0	4	N	1	1	9	N	N	N	N	1	1	1	1	127	114
99	2500	1	37	4	6	7	4	8	N	1	1	9	N	N	N	N	1	1	1	1	125	119
100	1105	1	36	9	9	7	0	0	N	1	1	1	N	N	N	N	1	1	1	1	115	107
101	1120	2	32	3	8	7	0	0	N	1	1	6	N	N	N	N	1	3	1	1	107	93
102	1100	2	32	7	8	0	0	0	N	1	1	6	N	N	N	N	1	3	1	1	109	95
103	970	2	31	5	8	7	11	0	N	1	1	1	N	N	N	N	1	2	1	1	125	106
104	790	1	30	2	7	7	12	0	N	1	1	1	N	N	N	N	1	2	1	1	107	91
105	2220	2	38	1	2	7	8	0	N	1	1	9	N	N	N	N	1	1	1	1	115	111
106	1520	2	38	6	9	7	14	0	N	1	1	9	N	N	N	N	1	1	1	1	94	91
107	1000	2	32	4	9	7	15	0	N	1	1	1	N	N	N	N	2	1	6	1	107	94
108	800	2	31	6	9	0	0	0	N	1	1	1	N	N	N	N	1	2	1	1	108	92
109	970	2	31	5	7	0	0	0	N	3	1	1	N	N	N	N	1	2	1	1	111	95
110	920	1	31	3	6	7	2	0	N	1	1	1	N	N	N	N	1	2	1	1	104	91
111	2300	1	34	3	8	0	0	18	N	1	1	5	N	N	N	N	3	4	6	4	.	.
112	880	1	34	3	8	0	0	0	N	1	1	1	N	N	N	N	1	2	2	7	.	.
113	1300	1	37	7	9	7	3	0	N	1	1	1	N	N	N	N	2	2	1	1	110	104
114	1950	1	34	6	3	0	0	6	N	1	1	3	N	N	N	N	1	2	1	1	105	95
115	1075	2	34	3	6	7	3	0	N	1	2	1	N	N	N	N	1	1	3	1	110	98
116	1200	2	31	2	4	7	13	3	N	1	1	1	N	N	N	N	1	2	4	1	121	102
117	1455	1	34	4	7	7	7	0	N	1	1	3	N	N	N	N	1	2	1	1	108	94
118	770	2	30	6	7	7	2	0	N	1	1	2	N	N	N	N	1	2	1	1	123	103
119	1200	1	30	5	8	0	0	0	N	1	1	1	N	N	N	N	1	1	1	1	105	91
120	1250	1	32	8	9	7	3	0	N	1	1	2	N	N	N	N	1	2	1	1	101	88
121	1170	1	34	2	8	0	0	0	N	2	1	1	N	N	N	N	1	1	1	9	.	.
122	800	2	29	9	9	0	0	0	N	2	1	1	N	N	N	N	1	2	1	1	107	88
123	1200	2	31	6	7	0	0	1	Y	1	1	2	N	N	N	N	4	2	1	1	86	74
124	1180	1	31	5	8	7	6	0	N	1	1	9	N	N	N	N	1	1	1	1	119	102
125	580	1	31	8	9	7	8	1	Y	1	1	1	N	N	N	N	4	3	1	1	96	84
126	870	1	30	7	9	7	15	0	N	1	1	1	N	N	N	N	3	2	1	1	120	100
127	850	2	30	2	5	7	14	0	N	1	1	1	N	N	N	N	1	2	1	1	109	90
128	1300	1	37	7	9	0	0	0	N	1	1	1	N	N	N	N	3	1	1	1	106	101
129	1160	1	31	4	6	7	14	10	Y	3	1	2	N	N	N	N	3	2	1	1	103	88
130	1300	1	34	1	5	0	0	5	N	4	1	1	N	N	N	N	1	1	5	5	.	.