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Title: Cerebral palsy in the West of Ireland and the application of the international criteria for the identification of acute intrapartum hypoxia: a cohort study.

A thesis presented to the National University of Ireland, Galway in fulfilment of the requirements for the degree of Doctor of Philosophy (Ph.D.)

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January 2012
Declaration

This thesis has not been submitted previously as an exercise for a degree at this or any other University. The thesis comprises only my original work towards the PhD except where indicated. Due acknowledgement has been made to all other material used.

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Patricia Healy
Summary

Background

Cerebral palsy is one of the most severe disabilities in childhood and occurs in 1-3 per 1,000 live births in Europe. This epidemiological study looked at a cohort of children with cerebral palsy to establish if their demographics, clinical characteristics and risk profiles are similar to those of other children with cerebral palsy described in the literature. The prevalence of variables associated with intrapartum hypoxia was also explored.

Methods

A retrospective cohort study was conducted. Data were extracted from maternal and neonatal records using a standardised data extraction form. Data analysis was conducted using SPSS (Statistical Package for the Social Sciences) version 18 and the Cochrane Review Manager Software (RevMan) (The Nordic Cochrane Centre, 2008).

Findings

One hundred children with cerebral palsy participated in the study. Singleton births accounted for 89% of the cohort and 11% were from multiple births. The gestational ages ranged from 24 to 42 weeks with 61% of the children being born at term and 39% born prematurely. Birth weights ranged from 780 grams to 4990 grams with 60% of the children having a normal birth weight and 40% being low birth weight. 84% of the children had a spastic subtype of cerebral palsy including, 34% with a spastic hemiplegia, 26% with a spastic diplegia and 24% with a spastic quadriplegia. Dyskinetic cerebral palsy occurred in 10% of the children and ataxic cerebral palsy in the remaining 6%. Many of the children had other impairments in addition to their motor difficulties. Among those additional impairments are, walking impairments (84%), intellectual impairments (62%), feeding difficulties (56%), epilepsy (44%), visual impairments (20%) and hearing impairments (13%). The likely time of origin of the cerebral damage was not classifiable in 13% of cases, antenatal in 38%, related to prematurity in 28%, neonatal and post-neonatal in 6% and followed intrapartum hypoxia in 15% of cases.

Conclusion

The distribution of antenatal, intrapartum and neonatal factors associated with cerebral palsy are similar to that found in other populations of children with cerebral palsy. The children have a distribution of cerebral palsy subtypes and associated impairments similar to other cerebral palsy cohorts. The study also found that the ACOG criteria for identifying acute intrapartum hypoxia sufficient to cause cerebral palsy were deficient.
Publications

In line with thesis submission guidelines, this thesis includes writings already published by me and which derive from my research work carried out during the period of my registration on the PhD register. These writings have been integrated into the body of this thesis.


Acknowledgements

This research thesis has been completed with the help, co-operation and understanding of many friends and colleagues, in particular:

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Dedication

I have decided to dedicate my PhD thesis to babies. Babies have been my constant companion and motivation throughout my career. So, I dedicate this PhD thesis to;

**My work babies** whose strength and resilience always amaze me. From my Crumlin days through my Coombe days I have met all kinds of babies. Conventionally perfect ones, unconventionally beautiful ones, big ones, small ones, cross ones, quiet ones, earthly survivors and other-world survivors and they have all been incredible.

**My Jack and Jill babies,** especially Fiachra and Amy, who have enriched my life by letting me into their families and homes.

**Cillian,** because you will always be part of my PhD journey.

**My family babies,** I am Auntie Trish to seven babies (so far!) and they fill me with joy and hope.

Hannah and Aine- the Bristol beauties

Mark, Evan and Nathan- the Carrigaline crew

Jack- a lover of food and tractors

Jacob- our latest arrival, who came a bit early and gave my family a living demonstration of what I do at work.

I am dedicating my thesis to babies because even after all this time and after all the thousands of babies I have met, the wonder of a new born baby still takes my breath away.
# Table of Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Declaration</td>
<td>iii</td>
</tr>
<tr>
<td>Summary</td>
<td>v</td>
</tr>
<tr>
<td>Background</td>
<td>v</td>
</tr>
<tr>
<td>Methods</td>
<td>v</td>
</tr>
<tr>
<td>Findings</td>
<td>v</td>
</tr>
<tr>
<td>Conclusion</td>
<td>v</td>
</tr>
<tr>
<td>Publications</td>
<td>vii</td>
</tr>
<tr>
<td>Acknowledgements</td>
<td>ix</td>
</tr>
<tr>
<td>Dedication</td>
<td>xi</td>
</tr>
<tr>
<td>Table of Contents</td>
<td>xiii</td>
</tr>
<tr>
<td>List of Figures</td>
<td>xvii</td>
</tr>
<tr>
<td>List of Tables</td>
<td>xix</td>
</tr>
</tbody>
</table>

### Chapter 1 Introduction

1.1: Background to the study | 1 |
1.2: Aim of the study | 4 |
1.3: Objectives | 4 |
1.4: Structure of the Thesis | 4 |

### Chapter 2 Literature Review

2.1 Introduction | 5 |
2.2 Literature Search | 5 |
2.3 Definition and Classification of Cerebral Palsy | 6 |
2.4 Cerebral Palsy Registers | 9 |
2.5 Epidemiology of Cerebral Palsy | 10 |
2.6 Risk factors and causal pathways for cerebral palsy | 12 |

#### 2.6 Risk factors and causal pathways for cerebral palsy

2.6.1 Antepartum risk factors and causal pathways | 14 |
2.6.2 Growth restriction as a risk factor | 14 |
2.6.3 Intrauterine infection and inflammation as a risk factor | 15 |
2.6.4 Gestational age as a risk factor | 17 |
2.6.5 Neonatal and post neonatal risk factors and causal pathways | 19 |
2.6.6 Intrapartum risk factors and causal pathways | 20 |
2.7 Cerebral Palsy and the Consensus Statement of the Cerebral Palsy Task Force | 32 |
2.8 Cerebral Palsy and Clinical Negligence Litigation | 34 |
2.9 Discussion and conclusion | 38 |

### Chapter 3 Methods

3.1 Introduction | 41 |
3.2 Aim of the study | 41 |
3.3 Objectives of the study | 41 |
3.4 Research Process | 41 |
3.4.1 Epistemology | 42 |
List of Figures

Figure 4.1 Summary of cohort recruitment process. ................................................................. 74

Figure 4.2 The distribution of cerebral palsy subtypes in the cohort ........................................ 82

Figure 4.3 Number of essential criteria satisfied by the cohort .................................................. 90

Figure 4.4 Number of suggested criteria satisfied by the cohort .............................................. 90
List of Tables

Table 2.1: Criteria to Define an Acute Intrapartum Event Sufficient to cause Cerebral Palsy........33
Table 3.1: Inter-rater agreement on a 60-item instrument by 5 expert reviewers used to assess content validity..........................................................55
Table 4.1: Details of the Maternal Sample.................................................................77
Table 4.2: Associations between risk factors and outcomes ........................................78
Table 4.3: Gestational age profile of the cohort.........................................................78
Table 4.4: Birth Weight profile of the cohort..............................................................79
Table 4.5: Birth Characteristics of the Cohort............................................................79
Table 4.6: Distribution of Apgar scores in the cohort.................................................79
Table 4.7: Association between Apgar scores and adverse outcomes............................80
Table 4.8: Resuscitation required at birth ................................................................80
Table 4.9: Distribution of neonatal encephalopathy in the babies with documented metabolic acidosis.................................................................80
Table 4.10: Incidence of neonatal encephalopathy stratified by gestational age.Error! Bookmark not defined.
Table 4.11: Distribution of neonatal illnesses in the cohort of babies admitted to the neonatal unit..........................................................81
Table 4.12: Differences in proportions of neonatal illnesses by gestational age .................82
Table 4.13: Distribution of the Cerebral Palsy Subtypes by gestation in the cohort..............83
Table 4.14: Differences in proportions of cerebral palsy subtype between the term and preterm babies........................................................................83
Table 4.15: Frequency of co-morbidities in the cohort....................................................84
Table 4.16: Frequencies of severe co-morbidities distributed by cerebral palsy subtype ....84
Table 4.17: Association between cerebral palsy subtype and severe co-morbidities ...........84
Table 4.18: Severe cases of CP stratified by cerebral palsy subtype...............................85
Table 4.19: Aetiology by likely time of origin...............................................................85
Table 4.20: Associations between antenatal aetiology and outcomes.............................85
Table 4.21: Associations between preterm aetiology and outcomes...............................86
Table 4.22: Aetiology by SCPE cerebral palsy classification.........................................87
Table 4.23: Associations between perinatal aetiology and outcomes.............................87
Table 4.24: Characteristics of term children with perinatal cerebral palsy .......................88
Table 4.25: Imaging findings of term children with perinatal cerebral palsy .....................88
Table 4.26: Presence of objective criteria in term children with perinatal acquired cerebral palsy...............................................................88
Table 4.27: Number of term perinatal cases meeting each of the 9 ACOG criteria .............92
Table 4.28: Distribution of cases meeting each essential criterion..................................88
Table 5.1 Major Pathologies associated with Cerebral Palsy........................................95
Table 5.2: Cerebral palsy distribution by gestational age and weight across 4 databases ........ 102
Table 5.3 Cerebral Palsy subtype distribution across 4 databases .................................. 108
Table 5.4 Distribution of additional impairments across 4 databases .................................. 109
Table 5.5 Distribution of severe cerebral palsy across 4 databases ...................................... 110
Chapter 1
Introduction

1.1: Background to the study

It is suggested that the above painting ‘The Healing of the Lame’ by Raphael from the year 1515, is probably one of the oldest paintings depicting a person with a contracture deformity in his lower limbs, probably cerebral palsy (Tonse, 2006; 249). Earlier references to cerebral palsy include descriptions of the Greek blacksmith god Hephaistos being mocked by other Olympians because of features consistent with spastic hemiplegia (Garland, 1995). It is believed by some that references in the Bible to people being ‘lame from the mother’s womb’ may refer to cerebral palsy (Obladen, 2011). Shakespeare’s 1591 play, Richard III, seems to suggest that King Richard III had a spastic hemiplegia. The quote in Act 1, scene 1, ‘deformed, unfinished, sent before my time; into this breathing world, scarce half made up; and so lamely and unfashionable that dogs bark at me as I halt by them’ has been interpreted as meaning that King Richard III was born premature and asphyxiated, required resuscitation and was left with a spastic hemiplegia (Accardo, 1980). Lord Byron (1788-1842), the British poet and leading figure in Romanticism, is believed to have had a spastic diplegia, although some argue that he had in fact a clubfoot and epilepsy.

The condition we now know to be cerebral palsy was described first in 1801 by the London surgeon and male midwife, Michael Underwood. In 1826, a Leipzig obstetrician, Johann Jorg, described the poor muscle tone associated with the condition. William John Little, an orthopaedic surgeon, described cerebral palsy further in a lecture series on deformities in 1843-44. William Osler was the first to use the actual term cerebral palsy in 1889. In 1893, Sigmund Freud first
suggested that not all cerebral palsy was associated with birth injury. He classified the aetiological factors associated with cerebral palsy into ante, intra and post-partum factors (Schifrin & Longo, 2000). Decades of research have continued since those early descriptions of cerebral palsy to give greater clarity and understanding to the condition. It is now acknowledged that cerebral palsy represents a group of disorders rather than a single disease entity. It is now understood as an abnormality of movement and posture secondary to a non-progressive lesion of a developing brain with a variety of associated risk factors and causal pathways.

Cerebral palsy is one of the most severe disabilities in childhood and makes heavy demands on health, educational and social services as well as on families and children themselves (Surveillance of Cerebral Palsy in Europe (SCPE), 2000). Despite advances in obstetric and neonatal care, the incidence of cerebral palsy has remained virtually unchanged at 2-2.5/1,000 live births worldwide for the past two decades (Nelson, 2003; Bax et al, 2005). In 2009, 76,021 babies were born in Ireland (ESRI, 2011) representing the highest birth rate since records began. Figures for the first quarter of 2011 again show a rise of 7.6% in the number of births (CSO, 2011). If the birth rate in Ireland continues to rise, and the incidence of cerebral palsy remains unchanged, then the absolute number of children with cerebral palsy in Ireland will continue to grow. Cerebral palsy will continue to pose a major clinical, psychosocial and financial challenge in current and future healthcare. Furthermore, while catastrophic birth injury is an extremely rare experience, cerebral palsy features strongly in clinical negligence litigation not least because of its devastating effect on the child and their family. Such litigation, irrespective of causation or outcome can be a traumatic experience for all concerned.

The cost of the clinical claims portfolio of the State Claims Agency has risen from €8.9 million in 2008 to €30.0m in 2010. However, while obstetric related claims account for approximately 25% of the number of cases reported to the Clinical Indemnity Scheme, they represent 60% of the value of claims (State Claims Agency, 2010). Cerebral palsy cases represent 3% of the total claims but account for a substantial proportion of the liabilities. This is due to the high costs of caring for children with cerebral palsy and the amount of money spent on servicing clinical negligence claims. Ireland’s receipt of financial assistance from its European counterparts has stimulated a renewed interest in, and focus on, the costs associated with clinical negligence and in particular that associated with cerebral palsy. The purse-holders of that financial assistance, the EU/IMF, under their Memorandum of Understanding, commit Ireland to taking steps to reduce the legal costs of the state. In response to a Dáil question about those legal costs, Deputy Michael Noonan, the minister for finance acknowledge that ‘The legal cost of the clinical claims portfolio has been increasing since 2008 due in particular to the resolution of high settlement value claims associated with cerebral palsy and other serious birth-related events’ (Noonan, 2011). Cerebral palsy is therefore a subject of interest for anyone involved in the maternity services because quite apart from the human interest aspect, our national government have indicated that the current costs of cerebral palsy are unsustainable.
Litigation concerning cerebral palsy usually relates to alleged negligence, particularly in the intrapartum period. However, a significant number of studies over the last two decades suggest that only a very small proportion of cerebral palsy is associated with intrapartum events. The proportion of cerebral palsy that may be attributed to intrapartum events is now estimated to be approximately 6-10% (Nelson & Grether, 1998; MacLennan, 1999; Stanley et al, 2000; American College of Obstetrics and Gynecology: ACOG, 2003) with 70-80% of cases being associated with antenatal events (Stanley et al, 2000). Despite this, the intrapartum period is often implicated in allegations of negligence. Identification of the timing of cerebral injury associated with cerebral palsy is crucial in cases where allegations of negligence are made. When establishing causation in cerebral palsy cases, the question to consider is whether brain injury is a direct consequence of actions or failure to act on the part of care providers. This implies that actions may prevent cerebral palsy. The ability to identify those cases of cerebral palsy that are not preventable has the potential to reduce significantly the legal costs of claims and potential awards for cases where the causation of cerebral palsy is not associated with care or negligence therein. Observational studies are instrumental in understanding factors associated with cerebral palsy and in understanding potential timings of cerebral injury. Understanding the associated factors for and timing of cerebral palsy may help isolate underlying contributing factors, which may be amenable to interventions aimed at minimising the risk of the occurrence of cerebral palsy. This study informs that understanding.

There is an abundance of literature on cerebral palsy in general, an increasing amount on cerebral palsy in Europe, but very limited publications on cerebral palsy in Ireland. Although cerebral palsy registers are identified as a key component in delivering an effective and efficient service, there is a dearth of publications relating to the Irish cerebral palsy registers. Data from the Irish cerebral palsy registers are submitted to the European register and presented as aggregated data in the International literature. However, there is a paucity of uniquely Irish data in both the national and international literature. The need for studies among the Irish population to provide a comprehensive picture of cerebral palsy in Ireland was the rationale behind this particular study.

This study uses a retrospective cohort design to explore data relating to cerebral palsy in the West of Ireland and will describe the prevalence, distribution and interrelationships of antenatal, intrapartum and neonatal variables associated with cerebral palsy in a cohort of children with cerebral palsy. These data will facilitate benchmarking of the demographics, clinical characteristics and risk profiles of children with cerebral palsy in Ireland with those with cerebral palsy in other jurisdictions in the developed world. The prevalence of variables in the cohort associated with acute intrapartum hypoxia is explored through the application of the ACOG (2003) criteria for the identification of acute intrapartum hypoxia. The ACOG criteria have not been applied previously to a European cohort and there are no previous Irish studies using the ACOG criteria. Many of the cerebral palsy studies conducted internationally look at antenatal or intrapartum or neonatal factors and their association with cerebral palsy. Many also look at either maternal or neonatal factors but not usually both. This may be a reflection of the professional practice area of the researchers.
conducting the studies. Current thinking supports the opinion that cerebral palsy arises from a combination of associated factors and intrinsic vulnerabilities. My combination of midwifery and neonatal clinical practice experience enabled me to combine maternal, neonatal, antenatal, intrapartum and post-natal aspects together in one study. This facilitated the production of a comprehensive picture of cerebral palsy and its associated factors. Nelson (2005) advocated just such a study when she advised that studies are needed that will connect the dots, putting together maternal characteristics, neonatal state, brain imaging findings and outcomes to provide information on pathways to disability.

1.2: Aim of the study
This study will describe the prevalence, distribution and interrelationships of antenatal, intrapartum and neonatal variables associated with cerebral palsy and apply the objective criteria for the identification of acute intrapartum hypoxia in a cohort of children with cerebral palsy.

1.3: Objectives
- To report the distribution of antenatal, intrapartum and neonatal factors associated with cerebral palsy in the cohort;
- To identify the availability of data in the maternal and neonatal records to facilitate application of the essential criteria for defining a causal relation between acute intrapartum events and cerebral palsy put forward by the Neonatal Encephalopathy and Cerebral Palsy Task Force Report (ACOG, 2003);
- To apply the ACOG (2003) criteria for defining acute intrapartum hypoxia in the cerebral palsy cohort.

1.4: Structure of the Thesis
The structure of this thesis is guided by the STROBE (strengthening the reporting of observational studies in epidemiology) guidelines on the reporting of epidemiological studies (Von Elm et al, 2007). The STROBE guideline provides a checklist of items that should be included in papers reporting on the design, conduct and findings of epidemiological studies, among them cohort studies (Appendix 1.1). The thesis is presented in six chapters. Chapter I, this introductory chapter, presents a brief background to the study, provides a rationale for the study and outlines the research aims and objectives. Chapter 2 critically evaluates the national and international literature on cerebral palsy with a specific focus on the antenatal, intrapartum and neonatal factors associated with cerebral palsy particularly acute intrapartum hypoxia. Chapter 3 provides a detailed description of the methodology and methods used to conduct the study. Chapter 4 presents the findings of the study. Chapter 5 critically analyses, discusses the findings, and places them in the context of the national and international literature. Chapter 6 outlines the conclusions reached and makes recommendations for education, practice, policy and future research arising from this study.
Chapter 2
Literature Review

2.1 Introduction

The following chapter explores a selection of literature relating to cerebral palsy. The condition we now call cerebral palsy was first described in detail by William Little in the 1860s when he published a paper linking obstetrical difficulties during childbirth with subsequent neurological damage in the infant. Little suggested that lack of oxygen to the brain due to complications in labour and birth leads to damage to the brain structures that control movement. The condition he described was initially referred to as “Little’s Disease”. The term cerebral palsy was first used by William Osler in the 1890s when he suggested associations between difficult birth, birth asphyxia and neonatal seizures. These early beliefs contributed significantly to the common assumption that intrapartum asphyxia was a significant contributing factor to cerebral palsy. However, we now know that intrapartum asphyxia alone accounts for only a small proportion of cerebral palsy. The best evidence from multiple clinical epidemiologic studies confirms that the overwhelming majority of cases of cerebral palsy do not result from isolated intrapartum asphyxia with resultant hypoxia and organ damage (ACOG, 2003). Evidence from decades of worldwide studies has found that the origins of approximately 70-80% of cases of cerebral palsy are likely to be antenatal, 5-10% is likely to be of neonatal or post neonatal origin with only approximately 10% accounted for by intrapartum factors (Stanley et al, 2000).

The chapter begins with a description of how the search of the literature was conducted and then goes on to expand on the literature identified.

2.2 Literature Search

The following literature review examines information relating to cerebral palsy. The following electronic databases were searched; Midwives Information and Resource Service (MIDIRS 1971-2012), Cumulative Index to Nursing and Allied Health Literature (CINAHL 1982-2012), and Medical Literature Analysis and Retrieval System Online (MEDLINE 1950-2012). A search of the Cochrane Database of Systematic Reviews (1992-2012) was also conducted. Searches were also undertaken of known cerebral palsy registers including both the European and Australian registers. No date limits were applied in the initial searches. Searches were made using appropriate database subject headings. The initial keywords utilised in the literature search were ‘cerebral palsy’, ‘spasticity’, ‘hemiplegia’ and ‘diplegia’. As the study developed, other key related terms such as asphyxia, encephalopathy, risk factors, epidemiology, incidence and prevalence were also used. These keywords were combined with the ‘and’ and ‘or’ Boolean operators as appropriate. Search delimiters were used where appropriate (for example title, abstract, keywords). Over 5,000 citations were identified from which abstracts were screened. The initial citations identified included papers on cerebral palsy topics as varied as Botox for hip pain, music therapy for irritability and marital breakdown among parents. Following screening, over 1,000 full-text papers considered relevant to
any aspect of this study were read in entirety. The researcher did not have a translation service available to her and therefore restricted the searches to English language resources only.

Extensive searches using manual discovery were also undertaken. Reference lists of accessed books and articles were searched to identify additional relevant literature. Available scholarly books and relevant PhD theses identified through the literature searches were also accessed through the National University of Ireland, Galway, library resources. Additional material was obtained through personal correspondence with selected authors. The literature reviewed was accessed periodically over the full course of this study from 2009-2012. Journals were monitored consistently to identify any new material relevant to the study. Following initial review of literature retrieved, the following areas emerged as relevant to this thesis:

- Definitions and classifications of cerebral palsy
- Cerebral palsy registers
- Epidemiology of cerebral palsy
- Risk factors and causal pathways of cerebral palsy
- Cerebral palsy and asphyxia
- Cerebral palsy and encephalopathy
- Cerebral palsy and the Consensus Statement of the Cerebral Palsy Task Force
- Clinical negligence litigation and cerebral palsy

2.3 Definition and Classification of Cerebral Palsy

Cerebral palsy is one of the most severe disabilities in childhood and makes heavy demands on health, educational and social services as well as on families and children themselves (SCPE, 2000). The early descriptions of cerebral palsy were based on clinical descriptions rather than any in-depth understanding of the aetiology and pathology of the condition. In 1959, the ‘Little Club’\(^1\) proposed a consensus definition describing cerebral palsy as “a persisting qualitative motor disorder appearing before the age of 3 years, due to non-progressive interference with the development of the brain” (Little Club, 1959: 28). Since then, numerous attempts have been made to define cerebral palsy with each seeking to provide a standard language for the process of identification (diagnosis) and provision of services (management) to meet the needs of those affected (Mutch et al, 1992; SCPE, 2000; Reddy, 2005).

Definitions and classifications of cerebral palsy have evolved over the decades as the condition itself and our understanding of it evolve. The main difficulty with defining cerebral palsy is that it cannot be considered a single disease entity but rather a collection of motor disorders of

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\(^1\)Little Club: Formed in 1957, the Little Club was an informal group of people with an interest in childhood disability who formulated a discussion document on terminology and classification of cerebral palsy.
heterogeneous origin (Mongan, 2006). It has been argued that cerebral palsy is not an entirely suitable term in that it refers only to a clinical description and infers nothing about aetiology, pathology or prognosis (Stanley et al, 2000; Carr, 2005). However, as a widely recognised and extensively used term, cerebral palsy remains in use. Stevens (2005) argues that it is important primarily that the term is kept for historical and cultural reasons and as a label accepted by those who have cerebral palsy. The most recent consensus definition suggested within Europe defines cerebral palsy as an umbrella term covering a group of non-progressive, but often changing disorders of movement and/or posture and of motor function, secondary to a non-progressive interference/lesion/abnormality in the developing immature brain (Surveillance of Cerebral Palsy in Europe (SCPE) 2000). To meet the criteria for the definition of cerebral palsy a child must be at least 4 years old. Children with recognised syndromes, brain abnormalities or chromosomal abnormalities are also included if they meet definitional criteria and have neurological signs of one of the subtypes of cerebral palsy (Jarvis et al, 2003). This definition is now widely used in Europe. Once a diagnosis of cerebral palsy has been confirmed, the cerebral palsy is then classified for epidemiological and clinical purposes.

The main problem associated with any classification of cerebral palsy is that it encompasses a heterogeneous collection of motor impairments with an array of clinical descriptions and varying aetiologies that are often poorly understood (Mongan, 2006). The traditional clinical terminology used to describe the subtypes of cerebral palsy has been confusing. Cerebral palsy has been classified by likely time of origin into prenatal, perinatal and postnatal causes. However, as a significant proportion of cerebral palsy may be of multifactorial aetiology acting at different times in fetal development, this classification is problematic (O’ Shea, 2008). The current terminology advocated by the collaborative group (SCPE), classifies cerebral palsy by the type of movement disorder; spastic, dyskinetic and ataxic. Spastic cerebral palsy refers to increased muscle tone and pathological reflexes and is the most common, accounting for about 80% of all reported cases. Dyskinetic cerebral palsy refers to abnormal patterns of posture and movement and affects about 10-20% of all cerebral palsy cases. Dyskinetic cerebral palsy can be further classified into two subtypes- choreo-athetosis or dystonia. Ataxic cerebral palsy refers to a loss of orderly muscular co-ordination with decreased muscle tone and affects about 5-10% of all cases (SCPE, 2000; Stanley et al, 2000). Mixed cerebral palsy refers to cases where different types of movement coexist. The number of limbs involved and whether the involvement is unilateral or bilateral may further classify cerebral palsy. Hemiplegia describes the unilateral impairment of the arm and leg on the same side of the body. Diplegia describes motor impairment primarily of the legs, which may or may not include some relatively limited involvement of the arms. Quadriplegia is the involvement of all four limbs (SCPE, 2000; Stanley et al, 2000).

Cerebral palsy may be further classified by describing the severity of the disability. Despite decades of cerebral palsy research, debate about how best to describe the severity of disabilities continues. Subjective terms such as mild, moderate, severe or profound are in common usage in publications of the last 20 years but are rarely defined clearly (Surman et al, 2006). Descriptions of the motor disability combined with descriptions of the functional disability are currently used to
describe the severity of cerebral palsy. SCPE advocates classifying severity by using walking ability as a crude measure of severity of motor disability. The levels of walking ability ascribed are; walks fluently, gait functional but non-fluent, gait obviously abnormal and no independent walking. Levels of functional disability are then categorised for additional impairments such as learning, hearing, visual and seizure activity.

In many individuals with cerebral palsy, impairments other than the motor impairments, interfere with their ability to function in daily life. Depending on the subtype of cerebral palsy, 25-80% of people with cerebral palsy have additional impairments (Odding et al, 2006). These impairments may have resulted from the same or similar pathophysiological processes that led to the motor disorder (Bax et al, 2005; O’Shea, 2008). Epilepsy is the most common additional disability along with learning difficulties. SCPE has reported that 31% of children with cerebral palsy have severe intellectual disability and 21% have epilepsy (SCPE, 2000). Standardised instruments are available to measure IQ, vision and hearing and categories describing specific levels of dysfunction have come to be generally accepted (Bax et al, 2005). These associated impairments are included in the SCPE classification system to help determine the level of severity of the cerebral palsy. The severity of the cerebral palsy, as determined by the motor disability and the additional functional impairments, has implications for quality of life and overall life expectancy. Mortality is strongly associated with the overall level of functional impairment, which depends on both the severity of the cerebral palsy as well as the associated impairments (O’Shea, 2008; Strauss et al, 2008). In a cohort study (n=2014) using a cerebral palsy database, Blair (2001) calculated risk ratios for mortality and found that the strongest predictor of mortality was intellectual disability. In a similar UK study (n=4007) Hemming et al (2005) concluded that the number and severity of impairments are the best predictors of survival in people with cerebral palsy.

The use of specialized registers and collaborative groups such as SCPE enables the formulation of a common language to describe, classify and research cerebral palsy and facilitates comparative research across international boundaries (Bax et al, 2005; Blair & Love, 2005). In addition, they also provide systematic coding for Health Information Systems (Reddy, 2005; SCPE, 2000). Epidemiologists in particular require consistent terminology and concepts across time and space in order to identify changing patterns of disease and disorder (Bax et al, 2005; Blair & Love, 2005). SCPE adopted a multidisciplinary approach to achieve its consensus on issues of definition and classification. They initially contacted 14 centres in 8 countries within Europe to participate in their collaborative group and all 14 centres subsequently registered data on children with cerebral palsy. One of 5 working groups subsequently established, focused on obtaining an agreed definition, description and classification of cerebral palsy that could be used by the network. Representatives from 10 of the 14 centres participated in that working group and an agreed consensus document emerged. A decision tree, which incorporated all these consensus views, was devised as a guide for participating centres to assist with describing and classifying cerebral palsy for inclusion in the European database (Appendix 2.1 & 2.2). Thus, Europe has a consensual description, definition and classification system for cerebral palsy cases.
There have been some criticisms of the standardised descriptions and classifications of cerebral palsy advocated by SCPE. During a meta-analytic review of prevalence, type, distribution and severity of cerebral palsy in relation to gestational age, Himpens et al (2008) found that the available literature (26 studies, n= 988,903) revealed that the classification of the clinical features was difficult and of relatively poor reliability. They suggested that even the consensual algorithm for type and topography of cerebral palsy as proposed by the SCPE (2000) left some distinctions between subtypes open for misclassification. Moreover, they advised that the algorithm had not, to the best of their knowledge, been proven reliable and had yet to be validated. In recognising that the validity and reliability of the guidelines had not been adequately assessed, SCPE subsequently tested the guidelines. The resulting study by Gainsborough et al (2008) tested the ability of coders to extract and interpret clinical information and their ability to apply the guidelines when classifying cerebral palsy cases. They found that there was a moderately good level of interobserver reliability and a substantial level of intraobserver reliability. The study found an encouraging level of agreement in assessing cerebral palsy cases for inclusion in registers but more variability describing cerebral palsy subtypes and level of functional disability. Gainsborough et al suggested that further work was needed to promote a shared understanding and use of the words and definitions used to describe the neurological and functional features of cerebral palsy. To strengthen the quality and consistency of data supplied to the database, SCPE have subsequently devised a single data collection form to use across registers. Gainsborough et al (2008) also advocated the incorporation of regular training and audit to improve adherence to SCPE guidelines. SCPE now provide a reference manual and training tool for registers to encourage consistency between clinicians and enable standardised description and classification of cerebral palsy and its subtypes (www.SCPE.com). Currently, the SCPE recommended descriptions and classifications of cerebral palsy are used for the West of Ireland Register referred to in this study.

2.4 Cerebral Palsy Registers

Although cerebral palsy is the most common childhood disability, it occurs in only 1-3 per 1,000 live births (SCPE, 2000) and so only a limited number of cases exist. Large populations are needed to amass sufficient numbers of subjects to answer research questions, particularly when studying subgroups of children with cerebral palsy. Specialised cerebral palsy registers capture data on a critical mass of cases and can therefore provide information about rates, causes and consequences of cerebral palsy and act as a valuable research resource. These specialised cerebral palsy registers now exist in several places around the world. The registers enable researchers to monitor epidemiological trends in the prevalence of cerebral palsy, provide valuable information about the associations between various factors and cerebral palsy, help improve the understanding of aetiology and measure the medical care and supportive services required by affected children and their families (SCPE, 2000; Mongan et al, 2006). The population-based registers are dependent on referrals from multiple sources to achieve optimum case ascertainment (McManus & Coghlan, 2005). Registers use multiple sources of case ascertainment including community and hospital based paediatricians and neonatologists, physiotherapists, health centres, general practitioners and child development organizations. There can be variability in the completeness of data over time and across geographically areas because the registers were set up
at different times, with some collecting data retrospectively and some collecting data about newly diagnosed children (Surman et al, 2006). Completeness of data is essential to ensure the validity of any epidemiological findings. This is especially true for cerebral palsy registers as the numbers with cerebral palsy are small and the exclusion of even a few cases can have a considerable effect on results. Generally speaking, having identified potential cases for the register, relevant clinical information is abstracted from obstetric and paediatric case notes. Each child is examined by a paediatrician and placed on the register when, at 5 years of age, a diagnosis of cerebral palsy is confirmed using the SCPE classification tree. It is recommended that children with clear signs of cerebral palsy who have died between the ages of 2 and 4 years are also included.

These registers are based in different geographical areas but data are often pooled so that large numbers will be available to allow differences and similarities to be investigated. In 1998, fourteen centres in eight European countries started a network of registers called the Surveillance of Cerebral Palsy in Europe (SCPE). The network includes registers from France, the UK, Denmark, Sweden, Germany, Ireland, Italy and the Netherlands. This type of closer collaboration should bring benefits from the pooling of expertise, the provision of a larger database enabling research not possible with smaller databases and a supportive network of colleagues familiar with similar issues (Surman et al, 2006). In the Republic of Ireland, there are three cerebral palsy registers. The East of Ireland Register covers counties Dublin, Kildare and Wicklow. The South of Ireland Register covers counties Cork and Kerry. The West of Ireland Register covers counties Galway, Mayo, Roscommon, Sligo, Leitrim and Donegal.

The West of Ireland Cerebral Palsy Register (WICPR) was accessed for this particular study. Established in 2002, the WICPR, initially collected data retrospectively to include all children born between 1990 and 2000 to mothers resident in the area. The SCPE descriptions and classifications of cerebral palsy are used by the WICPR. Data are stored on a confidential, computerised database that is managed by a named data controller. Parental consent is obtained before including a child on the register. For the birth years (1990-2000) included, the area covered by the West of Ireland Cerebral Palsy Register (WICPR) had a population of 81, 598 live births and 80,837 neonatal survivors. To date there are 136 children with cerebral palsy on the register.

2.5 Epidemiology of Cerebral Palsy

Epidemiology is the study of how often disease occurs in groups of people and why (Coogan et al, 2003). Prevalence and incidence are typical epidemiological measures undertaken to determine the frequency of occurrence of disease (Web et al, 2005). Prevalence refers to the number of existing cases of a disease and incidence to the number of new cases. These measures are very useful to determine the frequency and distribution of cerebral palsy across time periods, demographic groups and geographical areas. Thus, epidemiological data can illustrate trends of cerebral palsy or alert health practitioners to unusual clusters of events (Mulhall, 2000).

The worldwide prevalence of cerebral palsy ranges between 2 to 2.5 per 1,000 live births depending on the criteria used for inclusion (Stanley et al, 2000). Population studies have
established that rates of cerebral palsy have been consistent over the last few decades despite a fall in perinatal mortality rates. Nelson (2002) found that despite continuing drops in perinatal deaths and intrapartum injuries and a sharp decrease in ‘birth asphyxia’ as measured by low Apgar scores, there has been no net decrease in the occurrence of cerebral palsy among babies born at or after 37 weeks gestation over the past two decades. There are notable differences with regard to prevalence rates and factors related to cerebral palsy, between babies of varying gestational age and/or birth weight (Nelson, 2002). Along with the increased prevalence of cerebral palsy in the low birth weight infant it is also acknowledged that preterm birth is associated with a clear increase in risk of cerebral palsy (Nelson & Ellenberg, 1985; Pharoah et al, 1990; Murphy et al, 1997).

Term1 or near term2 babies constitute the majority of all births. Although term and near term babies are at relatively low risk for cerebral palsy compared with very preterm3 babies, they still make up at least one half of all cases of cerebral palsy (ACOG, 2003). The prevalence of cerebral palsy among low birth weight babies is higher than among normal birth weight babies. Babies of low birth weight (<2500 grams) are a very small proportion of the birth population but as a group they are at high risk of cerebral palsy, and constitute a disproportionate share of cases (ACOG, 2003). Following a meta-analytical review of 26 studies (n=988,903) looking at prevalence, type, distribution and severity of cerebral palsy in relation to gestational age, Himpens et al (2008) found that the prevalence of cerebral palsy decreases significantly with increasing gestational age from 27 weeks to term. Having analysed a large European dataset (n=2103), Platt et al (2007) concluded that extreme prematurity (< 28 weeks gestation) and very low birth weight (<1500g) are major risk factors for cerebral palsy, so much so that the epidemiology of cerebral palsy differs considerably between low birth weight babies and babies of normal birth weight.

Debate persists in the literature regarding whether or not there has been an increase in the prevalence of cerebral palsy in low birth weight and/or preterm babies. An increase in prevalence of cerebral palsy in low birth weight and/or preterm babies is associated with an increase in the functional severities of the disability. The debate persists because there have been discrepancies in findings from various studies related to the use of different denominators (live births or neonatal survivors) and the use of different birth weight specific groups and stratification by gestational age (Vincer et al, 2006; Robertson et al, 2007; Himpens et al, 2008). The most recent European data available from SCPE concludes that the prevalence of cerebral palsy among very low birth weight infants (<1500g) has remained stable or fallen during the 1990s (Platt et al, 2007). Milligan (2010) analysed 29 population-based studies looking at the outcomes of children born less than 32 weeks in Europe between 1983 and 2006 (n=16,358). He concluded that the continually improving survival of all but the most immature babies and the relatively constant rate of major disability (including cerebral palsy) mean that absolute numbers of children with significant disability

1 Term refers to babies of ≥ 37 completed weeks gestation.
2 Near term refers to babies of 34-37 weeks gestation
3 Preterm refers to < 37 completed weeks gestation
attributable to prematurity are increasing. However, the absolute number of children who survive without major disability is also increasing.

A number of studies have found that the prevalence of cerebral palsy is greater in multiple births than in singletons (Grether et al, 1993; Nelson & Ellenberg, 1995; Pharoah & Cooke, 1996; Pharoah & Dundar, 2009). In an epidemiological study of the European database (n=5,590) covering the birth years 1976-1990, Topp et al (2004) found a fourfold higher cerebral palsy rate in multiples compared to singletons. The risk of having a cerebral palsy affected child has been estimated to be 47 times higher for a woman with a triplet pregnancy (Petterson et al, 1993) and 8-12 times higher with a twin pregnancy compared to a singleton pregnancy (Grether et al, 1993; Petterson et al, 1993). Intrauterine death of a co-twin is associated with a 13-15 fold higher risk for cerebral palsy in the remaining twin, compared with twins who are both are born alive (Rydhstroem & Ingemarsson, 1993; Pharoah & Adi, 2000; Anand et al, 2006).

The higher risk of cerebral palsy in multiple births is closely related to low gestational age and low birth weight, two significant risk factors for cerebral palsy (Pharoah & Dundar, 2009). Multiple birth babies are more likely to be born prematurely and to be of lower birth weight than their term counterparts are. The total cerebral palsy rate in multiple births is about 4 times higher than in singletons. This difference largely reflects the higher proportion of singletons born at term. The rate of multiple births has increased in the developed world through the most recent decades largely due to rapid developments in fertility treatments and higher maternal age at first pregnancy. In their study of the European database, Topp et al, (2004) report that the multiple birth rate in Europe significantly increased from 1.9% in 1980 to 2.4% in 1990. They also found that the proportion of multiple births among all cerebral palsy cases increased from 4.6% in 1976 to 10% in 1990. This has significant implications for the epidemiology of cerebral palsy.

Changes in the epidemiological patterns of cerebral palsy have implications for the aetiology of the condition and for the health and social services provisions needed to care for children with cerebral palsy (Pharoah et al, 1996; Mongan, 2006). A fundamental problem in efforts to prevent cerebral palsy is a limited understanding of its causation. Although cerebral palsy is now recognised as a heterogeneous group of brain disorders with potentially different risk factors and causal pathways, understanding those varying aetiologies is vital as aetiology may influence outcome (Nelson, 2003; Tyson & Gilstrap, 2003; Wu et al, 2006).

### 2.6 Risk factors and causal pathways for cerebral palsy

Cerebral palsy is heterogeneous in both its manifestations and its causation. The aetiology of cerebral palsy remains unexplained in most cases. Pharoah et al (1996) suggest that it is likely that different aetiological factors acting at different times in fetal development are responsible for the

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1. Multiple births refers to all births with 2 or more babies
2. Singleton refers to births with one baby.
complexity of the abnormalities that comprise the syndrome. While a variety of ante, intra and postpartum risk factors have been identified for cerebral palsy; the precise aetiology may be difficult if not impossible to establish in many individual cases (Stanley et al, 2000; Paneth, 2001).

The nature and timing of events in the causal pathway leading to cerebral palsy remain a matter of debate. Brain imaging in the immediate neonatal period and/or later on may facilitate timing of the brain injury and help distinguishing ante partum from intrapartum from neonatal/ post neonatal injury (Truwit et al, 1992; Perlman, 1997; Ferriero, 2004; Bax et al, 2006; Krageloh-Mann & Horber, 2007; Robinson et al, 2008). Magnetic resonance images (MRI) obtained from children with cerebral palsy born at term have commonly demonstrated brain malformation such as agenesis of the corpus collosum or schizencephaly, known to have originated during pregnancy rather than during birth (Truwit et al, 1992). MRI obtained from children with cerebral palsy born prematurely has commonly demonstrated white matter damage of immaturity thought to occur before 34 weeks gestation (Bax et al, 2006). Cortical/subcortical damage or basal ganglia damage are typical MRI findings following intrapartum adverse events (Krageloh-Mann & Horber, 2007). Advanced methods of neuro-imaging have shown that events that affect the developing brain cause various abnormalities/lesions depending on the stage of brain development. They have also shown that different patterns of cerebral damage characterise different periods of compromise. It is also now recognised that different regions of the brain have different susceptibility to injury at different maturational stages. However, although neuro-imaging in the form of early neonatal CT (computed tomography) and MRI (magnetic resonance imaging) may provide information on the timing of an insult and help to characterise any resultant abnormality, in many instances it does not help to identify the cause of the insult.

The difficulty when studying risk factors and causal pathways for cerebral palsy lies in controlling for confounding factors. Confounding occurs when a separate factor (or factors) influences the risk of developing a disease other than the risk factor being studied. To be a confounder, the factor has to be related to the exposure and it has to be an independent risk factor for the disease being studied (Stewart, 2002). The association between exposure and outcome is distorted by the association between the confounder and both the exposure and outcome (Moon et al, 2000). This difficulty in controlling for confounding factors is a significant challenge in research examining cerebral palsy aetiology and associated risk factors. Typical confounders when studying cerebral palsy include low birth weight, third trimester bleeding and prematurity. Wu et al (2006: 696) recommend that only by separating infants into more homogeneous subgroups that reflect different underlying causal pathways can we gain additional insight into the pathogenesis of this poorly understood disorder. If practitioners were able to isolate underlying causal pathways and various contributing factors, interventions could be targeted at specific causal pathways that may lead to reductions in cerebral palsy prevalence.

Studies are complicated by differences in criteria used to select cases, different methods of controlling confounding (matching vs. regression), varying outcome data used, diversity of cerebral palsy classification systems and the distribution of infants across clinical subtypes (O Shea et al,
1998). Despite these inherent difficulties when conducting studies on cerebral palsy, a number of specific antepartum, intrapartum, neonatal and post neonatal risk factors associated with cerebral palsy have been identified.

2.6.1 Antepartum risk factors and causal pathways

Antepartum risk factors have been implicated increasingly as important determinants of the risk of cerebral palsy. It is now believed that some 70-80% of cerebral palsy cases are associated with antepartum events (Stanley et al, 2000). Increasingly, evidence is pointing to endocrine pathways, infection, coagulation defects, metabolic and autoimmune disorders or even a “vanishing twin” episode early in pregnancy as primary causes of many cases of cerebral palsy (Nelson & Grether, 1998; Wu & Colford, 2000; ACOG, 2003; Jarvis et al, 2003; Thorngren-Jerneck & Herbst, 2006). Associations between maternal thyroid disease, maternal seizures, environmental toxins, alcohol and illicit drug exposure and abnormal neurological development in the neonate have also been found. Investigators have suggested that maternal or fetal coagulopathies, or both, constitute important causes of lethal or disabling thrombosis before birth leading to cerebral palsy (Kraus & Acheen, 1999; Lynch et al, 2001). Several types of brain injury underlying cerebral palsy have been described, including brain malformations, hypoxic-ischaemic brain injury, focal arterial infarction and periventricular white matter injury (Hagberg et al, 2001; Wu et al, 2006). In some cases, the presence of antepartum risk factor may predispose infants to suffer acute brain injury during labour and birth (Wu et al, 2006). Growth restriction, intrauterine inflammation and gestational age are the antenatal risk factors that have consistently been found across studies.

2.6.2 Growth restriction as a risk factor

The terms intrauterine growth restriction (IUGR) and small for gestational age (SGA) are used to describe fetal growth that deviates from the normal. The terms are sometimes used interchangeably in the literature and incorrect use of the terms can often be confusing (ACOG, 2001; Kurjak et al, 2010). The term intrauterine growth restriction (IUGR) connotes an intrauterine pathophysiological process resulting in restriction of fetal growth (Haws, 2004). Small for gestational age (SGA) refers to newborns with a birth weight greater than two standard deviations below the mean for any gestational age (Haws, 2004). Growth restriction during pregnancy has been associated consistently with cerebral palsy (Jacobsson et al, 2002; Jarvis et al, 2003, 2005; Kurjak et al, 2010).

Analysis of a large (n=4503) collaborative European dataset by Jarvis et al (2003) shows that the rate of cerebral palsy in single births increases as intrauterine growth deviates either up or down from expected weight at that gestational age. Jarvis et al (2003: 1108) found that babies of 32 to 42 weeks gestation with a weight below the 10th percentile were 4-6 times more likely to have cerebral palsy than were those in the 25th–75th percentile reference band (RR 3.7 [3.2-4.3] to 6.3 [4.9-8.2]). In those with a weight above the 97th percentile, the increase in risk was smaller than that for the underweight babies (1.6 [1.1-2.2] to 3.1 [1.9-5.0]), but was still significant. Further analysis of the European dataset by Jarvis et al (2005) concluded that the severity of cerebral palsy was
consistently greater when intrauterine growth deviated from normal. They found that the greater the degree to which growth deviated either up or down from normal the higher the rate of cerebral palsy and the more severe the functional disability. Jarvis et al (2005) concluded that compared to those with normal intrauterine growth, the risk of more severe cerebral palsy is 16 times higher for those with a birth weight below the 3rd centile and 4 times higher when birth weight is above the 97th centile. Debate persists about the relevant clinical percentile threshold associated with an increased risk of adverse outcomes for the newborn (Badawi et al, 1998a). McIntire et al (1999) suggest that adverse perinatal outcome is confined generally to those newborns with birth weights below the 5th percentile and in most cases below the 3rd percentile. Odding et al, (2006) suggest that children below the 10th percentile are 4-6 times more likely to have cerebral palsy. While most newborns with IUGR do not sustain developmental delays or cerebral palsy, IUGR is linked closely to cerebral palsy even after adjustment for gestational age. This is true particularly for infants of extremely low birth weight, generally defined as those less than 1000 grams at birth (Clarke & Hankins, 2003).

As with many risk factors associated with cerebral palsy, the role of IUGR as an independent predictor is not completely defined (Chard et al, 1993). Uncertainty persists as to whether growth deviation is a cause or a consequence of cerebral palsy or simply an associated phenomenon (Jarvis et al, 2006). Stanley et al, (2000) suggest that the link between restricted growth and cerebral palsy might exist in either direction (i.e. abnormal growth causes cerebral palsy or vice versa) or through some confounding factor linked independently to growth and to the risk of cerebral palsy. Many factors associated with, or considered to serve as direct causes of IUGR, may also have an independent direct effect on neurological development (ACOG, 2003) and so it may be difficult to determine the exact order of association and effect. Among those factors are; congenital infections, substance abuse, coagulation disorders, pre-eclampsia and congenital abnormalities (Nelson & Ellenberg, 1985; Pharoah & Cooke, 1996; Grether & Nelson, 1997; Jarvis et al, 2006). Brain damage or maldevelopment in utero might trigger an abnormal growth pattern through endocrine or other pathways (Mongelli & Gardosi, 2000). Alternatively, the original cause of abnormal growth in utero might not be connected with damage to the developing brain but because abnormal growth increases physiological vulnerability, the brain is exposed to irreparable damage during or after delivery (Jarvis et al, 2003). Placental insufficiency with consequent reductions in fetal nutritive and oxygen supply is one of the most important causes of intrauterine growth restriction and fetal hypoxia. The placental insufficiency causes the intrauterine growth restriction and the growth-retarded fetus is then vulnerable to hypoxia, which exposes the baby to cerebral damage during and after birth. Each cause of growth restriction may differ in its relative impact or in predisposing the fetus to the damaging impact of an intermediate factor (ACOG, 2003) Thus, the precise nature of the link between IUGR and cerebral palsy as well as other neurological sequelae remains the subject of debate (Blair & Stanley, 1990; Uvebrant & Hagberg, 1992).

### 2.6.3 Intrauterine infection and inflammation as a risk factor

Abundant clinical evidence indicates that intrauterine exposure to maternal infection or inflammation is associated with a heightened risk of cerebral palsy and cerebral white matter
Congenital non-bacterial infections that may contribute to cerebral palsy include cytomegalovirus, enterovirus, human herpes virus 1 and 2, varicella-zoster virus and rubella as well as toxoplasmosis and congenital malaria (ACOG, 2003). A case-control study (n=688 cases and 3068 controls) conducted by Neufeld et al (2005) found increased risk of cerebral palsy (OR 3.1 [95% CI 2.3-4.2] for infants of women who had any infection during hospitalisation for delivery.

Mann et al (2009) (n=135,835) found that maternal genitourinary infection occurring in the first two trimesters was associated with increased risk of cerebral palsy in preterm or low birth weight children (OR 1.62, p<0.001). Murphy et al (1995) concluded, following a case-control study (n=59 cases, 234 controls), that ante and intrapartum risk factors associated with cerebral palsy are chorioamnionitis¹, prolonged rupture of membranes and maternal infection and this association persisted after adjusting for the confounding effect of gestational age. O’Shea et al (1998) reported an increased risk of cerebral palsy (Odds Ratio [OR] 2.4 [95% Confidence Interval (CI) 1.0-5.9]) associated with chorioamnionitis. Wu and Colford (2000) conducted a meta-analysis of 30 studies (n=6250) to evaluate the potential association between chorioamnionitis and cerebral palsy in both term and preterm babies. They found that clinical chorioamnionitis was significantly related to increased risk of cerebral palsy in term (Risk Ratio [RR] 4.7 [95% CI 1.3-16.2]) and preterm (RR 1.9 [95% CI 1.4-2.5]) babies.

Wu and Colford (2000) also found that clinical chorioamnionitis was significantly related to increased risk of periventricular leukomalacia (PVL) (RR 3.0 [95% CI 2.2-4.0]) in preterm babies. Cerebral white matter damage in the form of PVL is well recognised as an important antecedent to cerebral palsy (Perlman, 1998). PVL is considered to represent the typical response of the preterm brain to an insult. The relationship between chorioamnionitis, PVL and cerebral palsy and where PVL lies on causal pathways is still not clearly defined (Deng & Pleasure, 2008). The ACOG (2003) acknowledges that associations between histological and clinical chorioamnionitis, white matter lesions and PVL appear complex and are not yet understood completely. Wu et al (2003) suggest that several mechanisms may act together to cause the fetal brain injury in PVL. They suggest that elevated fetal cytokines cause direct injury to the fetal brain, inflammation of the placental membranes interrupts feto-placental gas exchange and maternal fever harms the fetal brain. The mechanisms of injury may differ between term and preterm babies. Genetic factors may, determine in part, the extent of inflammation that occurs in the face of maternal infection and intrinsic vulnerabilities in the developing fetal brain may have implications in the pathogenesis of subsequent cerebral palsy (Wu et al, 2003; Deng & Pleasure, 2008).

It is postulated that both subclinical and clinical chorioamnionitis can lead to a fetal inflammatory response and that this inflammation contributes to neonatal brain injury and subsequent cerebral palsy. Elevated blood and brain cytokine levels resulting from maternal infection lead, it is thought,

¹ Chorioamnionitis: inflammation of the chorion and amnion most commonly due to viral or bacterial infection.
to central nervous system damage in the fetus and possible subsequent cerebral palsy (Gomez et al, 1998; Wu & Colford, 2000; ACOG, 2003). Elevated concentrations of cytokines have been documented in the amniotic fluid of mothers of preterm infants who have chorioamnionitis. Studies are complicated by inherent difficulties in defining chorioamnionitis. Clinical signs such as maternal pyrexia, uterine tenderness, fetal tachycardia and malodorous amniotic fluid may indicate chorioamnionitis. However, to improve our ability to diagnose chorioamnionitis correctly, histological examination of the placenta is also needed along with the identification of microbial organisms from amniotic fluid or placental cultures (Wu & Colford, 2000; Wu et al, 2003). Studies confirm the existence of well-established histological features shown by the placenta in elucidating the aetiological processes leading to poor neonatal outcome (McDonald, 2002; Redline, 2005). Among those features are; inflammation of placental membranes, fetal vasculitis and fetal funisitis (inflammation of the umbilical cord). Standardised definitions of both clinical and histological chorioamnionitis would help researchers to understand better the relationships between chorioamnionitis, infection and cerebral palsy.

Further research is needed into this area because although it is accepted that intrauterine infection and inflammation are risk factors for cerebral palsy, not all infants exposed to intrauterine inflammation will develop cerebral palsy. Further, there is insufficient information to-date on the safe use of antibiotics in pregnancy for treating intrauterine infection. Studies by Nelson & Ellenberg (1985) and Kenyon et al (2008) concluded that perinatal exposure to antibiotics was associated with an increased risk of cerebral palsy. Kenyon et al (2008) found that more children whose mothers had received erythromycin (OR 1.93, [95% CI 1.21-3.09]) or co-amoxiclav (OR 1.69, [95% CI 1.07-2.69]) developed cerebral palsy than did those born to mothers who received no antibiotics. Nelson (2009) cautions that until the safety of antibiotics for the fetus/infant has been examined further, recommendations on treatment of infection in pregnancy or the newborn period should come, where possible, from high quality controlled trials.

2.6.4 Gestational age as a risk factor

Preterm birth is recognised as one of the strongest risk factor for the later development of cerebral palsy. The risk of cerebral palsy is inversely proportional to gestational age with rates being several times higher among preterm live births as compared with term live births (Joseph et al, 2003). A meta-analysis of 26 studies by Himpens et al (2008) concluded that the prevalence of cerebral palsy is 14.6% among infants born between 22 and 27 weeks gestation, 6.2% among those born between 28 and 31 weeks, 0.7% among those born between 32 and 36 weeks and 0.1% in term infants. Although only a small proportion of children are born prematurely, they, nevertheless, account for a significant proportion of cerebral palsy cases. However, controversy continues regarding the relationship between enhanced survival of preterm infants and the prevalence of cerebral palsy. It has been suggested by some that the number of preterm infants with cerebral palsy has increased since 1970, due to the parallel decrease in perinatal mortality related to advances in obstetric and neonatal care and the concurrent increase in the number of infants surviving with morbidities such as cerebral palsy (Murphy et al, 1995; Jacobsson et al, 2002). It has been suggested by others that cerebral palsy rates among low birth weight infants have actually
fallen in the 1990s (Surman et al, 2003; Platt et al, 2007). These conflicting findings are related to study design.

All studies report an excess of cerebral palsy in the preterm groups compared to the term population. Debate persists as to whether preterm cerebral palsy can be attributed to better survival of infants with an antenatal contributing factor for cerebral palsy or whether the impairment occurred intrapartum or neonatally in an infant already vulnerable because of prematurity (Tran et al, 2005). Murphy et al, (1997) suggest that adverse antenatal events contribute to some of the cases of preterm cerebral palsy and that others have their origins in adverse neonatal events or as a result of a continuum of adverse effects throughout antenatal and early neonatal life. Stanley et al, (2000) agree and suggest that the increase in preterm cerebral palsy reflects an increased survival in infants who have damaged brains at birth as a result of a range of antenatal factors, while it is also possible that the brain injury in the preterm follows complications in the neonatal period.

Intrauterine infection and inflammation are increasingly recognised as significant contributors to premature birth (ACOG, 2003). Preterm birth, in turn, is a significant risk factor for cerebral palsy. It has been proposed that fetal systemic inflammatory responses mediated by cytokines may precipitate the onset of labour in cases with intra-amniotic infection. Those fetal systemic inflammatory responses are also associated with brain lesions and cerebral palsy. Yoon et al, (2003) examined the relationship between umbilical cord plasma concentrations of cytokines at birth and the occurrence of PVL in 172 preterm births and demonstrated a significant association (OR 6.2 [95% CI 2.0-19.0]). Preterm babies with cerebral palsy often have brain lesions (intraventricular haemorrhages (IVH), periventricular leukomalacia (PVL)) related to the fragile nature of their cerebral blood vessels. These brain lesions are associated significantly with cerebral palsy. In a nested case-control study of 30 extremely preterm infants with cerebral palsy, Tran et al, (2005) concluded that PVL was the strongest predictor of cerebral palsy in extremely preterm infants. Han et al (2002) agree, noting that among preterm infants, PVL, defined as local necrosis in the white matter of the periventricular region, has been known to be the major causal lesion associated with neuro-developmental disorders, including cerebral palsy.

Despite multiple studies analysing antenatal risk factors for cerebral palsy in preterm infants, no single risk factor has been consistent across all or even most studies (Jacobsson et al, 2002). Maternal infection is a common cause of preterm birth but it is also a factor commonly associated with cerebral palsy. However, preterm birth may be associated with cerebral palsy through other non-inflammatory mechanisms, such as congenital abnormalities or growth retardation as well. The difficulty in interpreting the study findings associated with preterm infants' lies in determining which factors are causes of cerebral palsy and which are consequences of earlier disturbances in the antepartum and intrapartum periods and already part of the outcome. Murphy et al, (1997) controlled for adverse antenatal factors and mode of delivery and found that the strongest predictors of later cerebral palsy for very preterm babies are gestational age and abnormal neuroimaging findings. Future studies are needed to examine the independent associations
between neonatal complications and cerebral palsy by controlling for the presence of antepartum and intrapartum factors.

### 2.6.5 Neonatal and post neonatal risk factors and causal pathways

The term neonatal is used to refer to the first 28 days after birth. Post-neonatal refers to 28 days or more after birth. For 5-10% of children affected by cerebral palsy, there is a clear identifiable cause in the post neonatal period (Stanley et al, 2000; Cans et al, 2004). Among these causes are infections such as meningitis, encephalitis and septicaemia; head injuries including non-accidental injuries and road traffic accidents; vascular episodes such as cerebro-vascular accidents; surgical complications and others including near drowning and near miss cot death (Cans et al, 2004). The SCPE collaborative group has identified the dominant aetiological role of infection in post neonatal cerebral palsy accounting for 50% of cases and vascular episodes accounting for 20% of cases. However, this should be interpreted with caution as their data were limited by the relatively few children (n=347, 7.7% of the total cases) on the population-based registers with a post neonatal aetiology. Pharaoh et al, (1996) contend that it is likely that a high proportion of these post neonatal causes are potentially preventable by public health and other measures such as vaccination campaigns, childhood accident prevention campaigns and the avoidance of aspirin prescriptions for children because of the risk of Reye’s syndrome. Such measures have in recent years contributed to a decrease in the prevalence rates of post neonatal cerebral palsy from 2.19 per 10,000 for 1976 birth cohort to 0.62 per 10,000 for the 1990 birth cohort (Cans et al, 2004).

A number of case-control studies have identified factors in the neonatal period that are associated with the subsequent development of cerebral palsy. Murphy et al, (1997) conducted a case control study (n=59 cases, 234 controls) looking at neonatal risk factors in a preterm birth cohort. They found several cardiovascular, respiratory and systemic factors to be associated significantly with an increased risk of cerebral palsy. Among those neonatal factors were hypotension (OR 2.3, [95% CI 1.3-4.7]), patent ductus arteriosus (OR 2.3, [95% CI 1.2-4.5]), the need for a blood transfusion (OR 4.8, [95% CI 2.5-3.9]), prolonged ventilation (OR 4.8, [95% CI 2.5-9.0]), pneumothorax (OR 3.5, [95% CI 1.6-7.6]), sepsis (OR 3.6, [95% CI 1.8-7.4]), parenchymal lesions (OR 32.0 [95% CI 12.4-84.4]), ventricular dilatation (OR 5.4, [95% CI 3.0-9.8]) and seizures (OR 10.0, [95% CI 4.1-24.7]). The findings of Murphy et al suggest a role for several neonatal complications in the aetiology of cerebral palsy in preterm babies. In a nested case-control study of 30 extremely preterm (<28 weeks) infants with cerebral palsy, Tran et al, (2005) found that the three independent neonatal predictors of cerebral palsy were home oxygen use (OR 3.4, [95% CI 1.2-9.4]), moderate/severe ventricular dilation (OR 7.3, [95% CI 1.6-32.3]), and PVL (OR 29.8, [95% CI 5.6-59.1]). Walstab et al (2004) included both term and preterm infants in their case-control study (n=148 cases, 296 controls). Neonatal factors associated with the risk of developing cerebral palsy in the term infants were; cerebral lesions, meconium aspiration, sepsis, abnormal muscle tone and neonatal seizures. In the preterm infant, intraventricular haemorrhage (IVH), periventricular leukomalacia (PVL), sepsis, altered muscle tone and seizures were associated with an increased risk. These studies suggest that it is possible that the origins of cerebral palsy lie in the neonatal period for some children and especially for preterm infants. This has major implications for the provision of neonatal
care in that being able to identify possible neonatal factors allows prevention and intervention measures to be initiated in attempts to reduce the prevalence of cerebral palsy. However, the difficulty lies in being able to distinguish between neonatal factors that contribute to cerebral palsy and neonatal factors that are consequences of earlier antepartum or intrapartum events and already part of the outcome (Murphy et al, 1997).

2.6.6 Intrapartum risk factors and causal pathways

The proportion of cerebral palsy that may be attributed to intrapartum events is now estimated to be approximately 6-10% (Nelson & Grether, 1998; MacLennan, 1999; ACOG, 2003). In their large population-based, case-control study Badawi et al (1998b) found that an acute intrapartum event, a persistent occipitoposterior position and maternal pyrexia were all labour related events associated with a significantly increased risk of newborn encephalopathy and subsequent cerebral palsy.

There is a growing body of evidence that maternal fever in labour\(^1\) is an important factor associated with chorioamnionitis and the subsequent development of cerebral palsy in both preterm and term infants (Grether & Nelson, 1997; Nelson & Willoughby, 2002; Wu & Colford, 2000; Impey et al, 2001). Clinical and histological chorioamnionitis are strongly associated with maternal pyrexia in labour and adverse outcomes. Following a number of clinical studies, recognised inflammatory markers have been identified as mediators of central nervous system pathology including white matter lesions. These inflammatory markers include platelet activating factor, tumour necrosis factor, interleukin and cytokines (Wu & Colford, 2000; Mc Donald & McMenamin, 2001; McDonald, 2002). An association between maternal fever and encephalopathy has also been suggested in the development of cerebral palsy (Graham et al, 2008).

In addition to being associated with inflammation and chorioamnionitis, it is acknowledged that fever in labour is also associated with epidural analgesia, induction of labour, prolonged labour, oxytocin usage, nulliparity, instrumental delivery or infections other than chorioamnionitis (Nelson & Willoughby, 2002; Wu & Colford, 2000; Impey et al, 2001). These confounding factors present difficulties when studying the association between maternal fever in labour, intrauterine infection and adverse outcomes. Impey et al (2001) used logistic regression to control for various intrapartum factors in their prospective cohort study (n=4915 women) examining maternal fever and its association with neonatal encephalopathy. Their analysis showed that maternal fever in labour is strongly and independently associated with early neonatal morbidity, most significantly in the incidence of neonatal encephalopathy (OR 4.72 [CI 1.28-17.4]). However, they also conclude that maternal fever in labour may reflect an inflammatory response of multifactoral origin including autoimmune disease. Although intrauterine inflammation and infection is implicated in the development of cerebral injury and cerebral palsy, it is also implicated in the initiation of preterm labour, which is in turn a significant risk factor for cerebral palsy. Wu & Colford (2000) note that

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\(^1\) Maternal fever: temperature > 38 degrees Celsius on two or more separate occasions during labour.
although gestational age appears to be a possible confounder, it may also lie directly in the causal pathway between maternal infection and cerebral palsy. Thus, while it is now accepted that maternal fever in labour and maternal infection is strongly associated with neonatal encephalopathy and cerebral palsy, further studies are needed to establish intrapartum fever as an independent risk factor (Nelson & Willoughby, 2002; Wu & Colford, 2000; Impey et al, 2001).

The intrapartum risk factor and causal pathway most often implicated in cerebral palsy is intrapartum asphyxia.

### 2.6.6.1 Cerebral Palsy and Asphyxia

Intrapartum asphyxia was first suggested as a risk factor and element in the causal pathway of cerebral palsy by William Little in 1862. Little’s seminal paper on the relationship between perinatal events and motor and cognitive deficits in children ‘The influences on the mental and physical condition of a child’ stated that:

> the object of this communication is to show that the act of birth does occasionally imprint upon the nervous and muscular systems of the nascent infantile organism very serious and peculiar evils’  

(Little, 1862, pg 293).

Intrapartum asphyxia has been written about extensively since then and for many years its importance as a direct cause of cerebral palsy was overestimated (Tyson & Gilstrap, 2003).

Asphyxia refers to the impairment of blood gas exchange leading, if it persists, to progressive hypoxaemia (lack of oxygen in arterial blood) and hypercapnia (accumulation of carbon dioxide). Hypoxia refers to the inadequate oxygenation at cellular and tissue level that follows asphyxia (Boxwell, 2000; Fahey & King, 2005). Significant asphyxia results in anaerobic metabolism, which in turn leads to an accumulation of lactic acids, which gives rise to metabolic acidosis (Bax & Nelson, 1993). Although the relationship of asphyxia to the subsequent development of irreversible brain damage remains poorly defined it is known that significant asphyxia contributes to hypoxic ischaemic brain injury (Freeman & Nelson, 1988; Fahey & King, 2005).

In spite of earlier assumptions, it is now acknowledged that intrapartum asphyxia plays only a small part in the aetiology of cerebral palsy (Blair, 1993; Gaffney et al, 1994; Nelson & Grether, 1998; Bakketeig, 1999; Hankins, 2003). Intrapartum asphyxia incidence rates of between 2 to 9 per 1,000 live births have been reported (Thornberg et al, 1995; Wu et al, 2004). Low (2004), having examined the blood gas and acid-base status of 23,000 babies at birth, reports the prevalence of birth asphyxia in the term infant at 26 per 1,000 live births with only 15% of those being in the moderate to severe range. He reports the prevalence of asphyxia in preterm infants as 73 per 1,000 live births of which 48% were in the moderate to severe range. Incidence rates of asphyxia vary between studies depending on how the asphyxia is defined and how the study population is selected. Intrapartum asphyxia is diagnosed in approximately 8 to 20% of cerebral palsy cases (Pschirrer & Yeomans, 2000; Stanley et al, 2000; Clarke & Hankins, 2003; Fahey & King, 2005).
Increasingly, the debate about the aetiology of perinatal brain injury emphasises the relatively small contribution of the intrapartum period and it is now broadly accepted that in most cases the genesis of asphyxia and hypoxic ischaemic cerebral injury of cerebral palsy is before labour and delivery (Perlman, 1997; Badawi et al, 1998b; Stanley et al, 2000; Krageloh-Mann & Cans, 2009). Potentially asphyxiating conditions in the antenatal period have been identified as ante-partum haemorrhage, placental infarctions, umbilical cord incidents, maternal shock, infection, diabetes, intrauterine growth restriction and prematurity (Badawi et al 1998a; Low, 2004). In most cases the aetiology of asphyxia is idiopathic. The difficulty is in deciphering if the asphyxia was part of the initiating pathology or a consequence of a chain of pathological events.

Intrapartum asphyxia is still often implicated as a significant contributing factor to subsequent cerebral palsy. There are a number of acute, catastrophic events that may occur during labour that can contribute to an asphyxial insult (ACOG, 2003; Berglund et al, 2010). These acute intrapartum events are noted in the ACOG (2003) consensus statement as: umbilical cord prolapse, shoulder dystocia, uterine rupture and maternal cardiopulmonary arrest. Any of these acute events may result in neurological morbidity and sequelae but this outcome is not certain. Normal outcomes have been reported following prolonged asphyxia and vice versa. The fetus can compensate to some extent for an asphyxia exposure but if the insult continues, will reach a threshold at which cerebral and neurological damage will occur. It is thought that vulnerability to damage from asphyxia is mediated by different characteristics in the fetus such as gestation and intrauterine growth but it is not known how much asphyxia a fetus can tolerate and for how long before damage occurs (Low, 2004; Fahey & King, 2005). The physiological reserves in a fetus can be compromised in situations of post maturity, intrauterine infection, thick meconium in the amniotic fluid and reduced volumes of amniotic fluid. Any of these factors may increase the fetus’s vulnerability to asphyxia.

The critical ischemic threshold for neuronal necrosis in the developing brain remains unclear (Perlman, 1997). Data that are available from studies over the years are limited by virtue of the fact that most of the studies were animal studies involving sheep and monkey fetuses. It is now known that the sheep and monkey fetus has a different neurological maturity than that of the human fetus (Longo, 1997; Low, 1997 & 2004). Maturity of cerebral neurons plays a part in the cerebral response to asphyxia. As well as the actual asphyxia; hypotension, hypovolaemia and tissue perfusion are critical in the development of neurological damage. However, even when asphyxia is prolonged or severe, most newborn infants recover with minimal or no neurological sequelae (Perlman, 1997). The outcomes of studies into intrauterine asphyxia have been variable, ranging from no brain damage, to brain damage in some, to fetal death in some. Thus, not all babies who experience intrapartum asphyxia are destined for a later diagnosis of cerebral palsy.

Perlman (1997: 854) contended that infants with intrauterine asphyxia might present in one of four ways:

1) There may be no symptoms either antepartum, during labour or in the neonatal period;
2) There may be no antepartum symptoms but intrapartum problems may be encountered such as meconium stained amniotic fluid or fetal heart rate abnormalities;
3) There may be no antepartum symptoms but the newborn may display signs of intrapartum distress such as low Apgar scores, the need for resuscitation or neonatal encephalopathy;
4) All 3 scenarios may be preceded by antenatal events known to be associated with brain injury.

Since Perlman wrote this paper, it has been widely acknowledged that these “symptoms” of asphyxia and resulting hypoxic ischemia have low predictive value for and lack sensitivity and specificity in diagnosing asphyxia and subsequent cerebral damage (Nelson & Grether, 1998; ACOG, 2003). Asphyxia is now known to be an imprecise and nonspecific general term. Asphyxia has been described by Wu et al (2003:2678) as a ‘vague and controversial term that denotes a clinical diagnosis lacking specificity for any single underlying pathological condition’. For many years, the American College of Obstetricians and Gynecologists (ACOG, 1993, 2004 & 2005) has been recommending replacing the term birth asphyxia with terms referring to clinically observable events. Difficulties persist in reaching a clinically operational definition and there is currently no readily available tool for the direct measurement of asphyxia. Therefore, it continues to be commonly inferred based on various fetal and neonatal signs including, intrapartum fetal heart rate patterns, low Apgar scores, meconium staining of amniotic fluid, acidosis and neonatal seizures.

2.6.6.1.1 Fetal heart rate patterns as an indicator of asphyxia

The most widely used chief indicator of possible asphyxial events in labour has been fetal heart rate patterns. Fetal heart rate monitoring was initially designed to detect changes in heart rate that might identify asphyxia in utero and hence infants at greatest risk of developing hypoxic-ischemic cerebral injury. However, despite a two-decade experience of intensive use of fetal heart rate monitoring the impact on subsequent neurological and cognitive outcome has been minimal (Nelson, 1998; Greene, 2006). There is no evidence to-date of a difference in perinatal mortality or on cerebral palsy rates with the use of fetal heart rate monitoring (Devane et al, 2010). Cochrane systematic reviews have concluded that the introduction and widespread use of electronic fetal monitoring in labour, with or without fetal blood sampling, has not been shown in randomized trials to decrease perinatal mortality, intensive care admission or low Apgar scores (Thacker et al, 2001; Alfirevic et al, 2006).

Interpretations of fetal heart rate patterns have been found to be highly inconsistent with a low predictive value (Herczeg, 1997; Miller 2011a). Whereas fetuses that are severely asphyxiated during the intrapartum period will have abnormal fetal heart rate patterns, most patients with non-reassuring fetal heart rate patterns give birth to neonates with normal Apgar scores (Nelson et al, 1996). In fact, abnormal electronic fetal heart rate patterns have been found to be poor predictors of the subsequent development of cerebral palsy (Nelson et al, 1996). The most frequently observed abnormal fetal heart rate pattern associated with cerebral palsy are those with multiple late decelerations and decreased baseline variability (Schifrin, 2004; Schifrin & Ater, 2006; Chandraharan & Arulkumaran, 2007; Arulkumaran & Gibb, 2008). However, even those patterns have a false positive rate as high as 99.8% and therefore, cannot reliably predict hypoxia or
cerebral palsy (Nelson et al, 1996; Fahey & King, 2005). It is now accepted that abnormal fetal heart rate patterns observed during labour may actually reflect pre-existing neurological injury of the fetus that cannot be ameliorated by intrapartum interventions. Abnormal fetal heart rate patterns may also reflect the effects of medications, fetal anomaly, fetal injury and infection and not just hypoxia (Pateman et al, 2008).

Several studies of CTG interpretation have shown significant variation between individual practitioners interpreting the same tracing (inter-rater) and between interpretations by the same individual when they examine the same tracing on successive occasions (intra-rater) (Ayers-de-Campos et al, 1999; Blix et al, 2003; Devane and Lalor, 2005). It is not uncommon for obstetricians to face litigation for negligence for what is believed to be brain damage due to birth asphyxia because of 'inaccurate' interpretation of CTG traces. In many cases, experts are unable to agree on the significance of CTG changes, whether the injury occurred before or during labour or whether it could have been prevented by emergency delivery (Umstad, 1995; Nelson et al, 1996). When looking at inconsistencies among experts around CTG interpretation, Ayers-de-Campos et al (1999) found that individuals who were considered expert agreed on approximately 60% of normal fetal heart rate patterns but only 25% of pathological patterns. Devane and Lalor (2005) examined the intra- and inter-observer agreement in midwives’ visual interpretation of intrapartum cardiotocographs (CTGs). They found that overall intra-rater agreement ranged from 'fair to good' (Cohen’s Kappa (k) = 0.48) to ‘excellent’ (k=0.92). Inter-rater agreement was ‘fair to good’ (k = 0.65- 0.74). They concluded from their study that levels of agreement revealed degrees of variation that expose room for improvement.

The American College of Obstetrics and Gynaecology (ACOG, 2004) contend that the diagnosis of fetal distress from the interpretation of a CTG is imprecise, non-specific and has low positive predictive value. They advocate that the more objective term non-reassuring fetal status is more appropriate to reflect accurately the clinician’s interpretation of data regarding the fetal condition (ACOG, 2004). Greene (2006) suggests that a nonreassuring fetal heart rate pattern should be seen as an imperfect screening test for intrauterine asphyxia rather than as a diagnostic test for asphyxia and its sequelae. Electronic fetal monitoring alone is not a precise tool for the identification of intrapartum asphyxia and other additional or alternative forms of intrapartum monitoring will have to be developed to identify accurately the asphyxiated infant in utero (Borruto et al, 2007; Larma et al, 2007).

2.6.6.1.2 Apgar Score as an indicator of asphyxia

The Apgar score describes the condition of an infant at birth. Traditionally, the Apgar score has been used as a criterion for the diagnosis of birth asphyxia but this is now known to be inappropriate (American Academy of Pediatrics (AAP), 2006a). The value of the Apgar score as a prognostic tool has also been widely debated. Some studies have found associations between Apgar scores and neonatal outcome, including cerebral palsy (Moster et al, 2001; Kveim et al, 2010) while others have reported weak or non-significant associations (Jacobsson et al, 2002; Walstab et al, 2004; Tran et al, 2005). Many factors, other than asphyxia in labour, can affect
Apgar scores including infection, maternal medication, physiological maturity of the infant and underlying neurological abnormalities (Marlow, 1992; Papile, 2001). The presence of a low Apgar score as an isolated criterion is not indicative of intrapartum asphyxia and several studies have demonstrated both false-positive and false-negative results for intrapartum asphyxia with its use (Nelson & Ellenberg, 1981; Ellenberg & Nelson, 1988; Moster et al, 2001).

Several studies have been conducted to examine the ability of the Apgar score to predict further progress reliably (Moster et al, 2001; Thorngren-Jerneck & Herbst 2001; Moster & Markestad, 2007; Kveim et al, 2010). More recent studies have found significant association between low Apgar scores and cerebral palsy in children born at term or with normal birth weight, whereas studies in children with a low birth weight or born preterm have shown conflicting results (Kveim et al, 2010). Thorngren-Jerneck and Herbst (2001) performed a population-based study on over 1 million term births in Sweden looking at Apgar scores. They found that a 5-minute Apgar score under 7 in term infants was associated with an increased risk of neonatal morbidity (OR 5.87 [CI 3.43-10.0]), infant mortality (OR 14.4 [CI 12.5-16.5]) and neurological impairment (OR 31.4 [CI 27.3-36.1]). In a case-control study with a preterm birth cohort (n=59 cases, 234 controls), Murphy et al (1997) found that an Apgar score ≤ 3 at 5 minutes was significantly associated with an increased risk (OR 5.3 [CI 1.4-21]) of cerebral palsy. Kveim et al (2010) explored the association of cerebral palsy with Apgar score in both low and normal birth weight babies (n= 543,064). They found a strong association in the normal birth weight children (OR 53.1 [CI 35-80]) and a moderate association (OR 20 [CI 14.5-29]) in the low birth weight children. Differences in cut off points used to diagnose ‘low’ Apgar and variability in birth weight specific groups means that further studies are needed to confirm these initial findings.

Although further in-depth studies are needed to clarify the association between low Apgar scores and subsequent cerebral palsy it does seem that a persistent low Apgar scores at 5, 10 and 20 minutes are associated with increasing mortality and morbidity (American Academy of Pediatrics, 2006b). Review of the literature revealed that overall the Apgar score appeared to be a moderate level predictor for neonatal deaths and the development of cerebral palsy, with the 5, 10 and 20 minute Apgar having better predictive value than the 1 minute score. However, as a stand-alone tool the Apgar score is not a specific indicator for intrapartum compromise or a good predictor of adverse neurological outcome. Thus, the Apgar score alone cannot be considered evidence of, or a consequence of, asphyxia. Many children with cerebral palsy have not had low Apgar scores at birth and many children with low Apgar scores at birth do not go on to develop cerebral palsy (Moster & Markestad, 2007).

2.6.6.1.3 Meconium staining as an indicator of asphyxia

Like the Apgar score, meconium staining of the amniotic fluid has been traditionally used as a marker for newborn asphyxia or hypoxia. However, like the Apgar score, it is a poor predictor of long-term neurological disability, especially cerebral palsy, in the term infant (ACOG, 2003). Meconium stained amniotic fluid affects approximately 20% of infants the vast majority of whom do not develop cerebral palsy (Nelson & Grether, 1998). In-utero meconium passage rarely occurs
before 32 weeks of gestation and most babies with meconium stained amniotic fluid are 37 weeks gestation or older, with increasing incidence as gestational age increases (Ahanya et al, 2004). Meconium in the amniotic fluid has been suggested to stimulate umbilical vessel constriction, tissue necrosis and production of thrombi potentially associated with fetal hypoxia and ischemic cerebral palsy (Altshuler & Arizawa, 1992). Earlier studies suggested that meconium passage in conjunction with abnormal fetal heart rate increased perinatal morbidity and mortality rates (Krebs et al, 1980) although more recent studies have not supported these findings (Richey et al, 1995; Jazayeri et al, 2000). Some commentators consider thick meconium to reflect in-utero stress (Ziadeh & Sunna, 2000) while others question the association of meconium with fetal hypoxia, acidosis or asphyxia (Ciftci et al, 1999). Controversy persists regarding the significance of meconium stained amniotic fluid. The traditional belief that an element of chronic hypoxia contributes to the passage of meconium in utero has been somewhat replaced by the suggestion that the accumulation of meconium in the amniotic fluid is actually secondary to impaired clearance from decreased swallowing (Nathan et al, 1994; ACOG, 2003). Ahanya et al (2004) conclude that further research is required to understand the role of chronic hypoxia, infection and other fetomaternal stress factors in the passage of meconium in utero. In the meantime, meconium staining of the amniotic fluid does not represent a reliable indicator of fetal condition or potential outcome.

2.6.6.1.4 Acidosis as an indicator of asphyxia

Acidosis, as an indicator of intrauterine asphyxia, is assessed by analysis of fetal or umbilical blood gas and acid-base status. Earlier studies exploring the relationship of acidosis at birth, defined by umbilical arterial blood, with subsequent neurological outcome have conflicting findings (Perlman, 1997; Schifrin, 2004). However, studies that are more recent have provided some clarity. Malin et al (2010) performed a systematic review and meta-analysis (51 studies, n=481753 infants) in which umbilical cord pH at birth was compared with neonatal and long-term outcomes. They found that a strong, consistent and temporal association exists between low umbilical arterial pH at birth and major adverse outcomes including death (OR 16.9 [CI 9.7-29.5]), hypoxic ischaemic encephalopathy (OR 13.8 [CI 6.6-28.9]), serious brain abnormalities (OR 2.9 [CI 2.1-4.1]) and cerebral palsy (OR 2.3 [CI 1.3-4.2]). Malin et al (2010) do acknowledge, however, that the studies they pooled had heterogeneity in terms of quality, population risk, threshold of cord pH used and ascertainment of neonatal outcome. In studies of exposure to fetal asphyxia, a consistent finding before brain damage occurred has been a severe metabolic acidosis (Low, 2004). The magnitude of the changes in the blood gas values obtained from the cord umbilical artery that define potentially damaging birth asphyxia remains controversial and the umbilical arterial pH that best indicates asphyxia remains unclear (Helwig et al, 1996; Perlman, 1997; Schifrin, 2004). Although the precise value that is required to define damaging acidaemia is not universally agreed on, a consensus has been reached which considers a pH less than 7.20 to be indicative of fetal acidaemia (Sehdev et al, 1997) and a pH less than 7.0 to realistically represent clinically significant acidosis (Jasper and Arulkumaran, 2000; ACOG, 2003; Armstrong & Stenson, 2007). Similarly, there is no consensus on the level of base deficit that defines metabolic academia. The most common cut-off values used are base deficit >12 mmols (Low, 1997; Jasper & Arulkumaran, 2000; ACOG, 2003).
The risk of poor neonatal outcome increases in newborns with umbilical blood gas values that reflect a metabolic acidosis, namely a low pH and an elevated base deficit. However, while pH and base deficit evidence of a significant metabolic acidosis may indicate that exposure to asphyxia has occurred it does not necessarily reflect the nature, duration and severity of the fetal exposure nor does it necessarily reflect outcome. Most infants with evidence of intrapartum acidosis do not develop serious long-term sequelae. It must also be considered that acidaemia could be a response to exogenous stimuli such as maternal acidaemia, regional anaesthesia or uterine contractions and well within the adaptive capacity of the fetus rather than a reflection of a serious morbid fetal state (Goodlin, 1995:1831). Rennie et al (2007) also caution about the possibility of venous samples being incorrectly labelled as arterial and therefore not being a reliable indicator of acidosis. In clinical practice, analysis of paired arterial (blood direct from the fetus) and venous samples (blood from the placenta) is recommended to ensure that true arterial measurements as opposed to venous are obtained (Armstrong & Stenson, 2007; Neilson, 2010).

The presence of severe fetal acidaemia, while a distinct marker of fetal compromise, does not provide insight with regard to the fetal adaptive ability to maintain cerebral perfusion (Perlman, 1997; Fahey & King, 2005). The limited access to a fetus antenatally makes it very difficult to study fetal asphyxia, its duration, whether it was acute or chronic and its affect on cerebral blood flow. It was believed initially that the presence of acidosis in the umbilical cord arterial blood would be a good measure of the severity or duration of the intrauterine asphyxia and would correlate with outcome but this has not been demonstrated (Ross & Gala, 2002; Ross, 2011). Work continues to identify or develop an accurate, continuous, non-invasive method of measuring fetal wellbeing in the intrapartum period. Attention is focused currently on measuring umbilical cord lactate, which has been shown to correlate with both pH and base excess (Kruger et al, 1998; East et al, 2010). The definitions of acidaemia and its diagnosis can become very important in situations where clinical negligence is alleged in cases of cerebral palsy. The legal courts may look at the timing and results of these tests in determining causation. It is now common in clinical practice to recommend umbilical cord blood gas analysis in all high-risk births to facilitate assessment of the infant's condition at birth. Despite the limitations of the analysis of fetal blood gas and acid-base status, the most objective current assessment available of the presence of fetal asphyxia is metabolic acidosis in umbilical arterial blood at the time of birth (ACOG, 2006; Graham et al, 2008).

2.6.6.1.5 Fetal and neonatal markers as indicators of asphyxia
Thus, it seems that the markers, outlined above, that have been accepted traditionally to indicate asphyxia in the newborn are actually individually non-specific and imprecise. Clinical studies have found that there is limited correlation between current markers of intrapartum asphyxia and subsequent neurological outcome (Curtis et al, 1988; Korst et al, 1999). This creates barriers for care providers in identifying and managing compromised infants. It also creates enormous potential for misclassifying an infant as having sustained damaging intrapartum asphyxia and this may have very serious implications from a litigation perspective when determining causation, preventability and liability. Perinatal asphyxial events can cause newborn neurological damage and cerebral palsy. However, intrapartum compromise can be simply a reflection of antenatal fetal pathology.
and vulnerability to intrapartum compromise may depend on fetal characteristics such as gestational age and fetal growth. The difficulty lies in identifying the causal factors for intrapartum asphyxia reliably and independently from other causal factors. Schifrin (2004) contends that the current understanding of the relationship of markers for intrapartum asphyxia to subsequent neurological injury reveal that various markers such as, acidosis, encephalopathy and abnormal fetal heart rate patterns, indeed increase the risk of subsequent disability. The problem, according to Schifrin, is that we do not understand the different possible mechanisms, timing and outcomes of asphyxial injury. It is not known how much perinatal asphyxia is primary and how much is a secondary consequence of other pathologies. Using the markers of fetal compromise currently available to us, we cannot define reliably which of these infants have pre-existing antenatal neurological damage that may be unrelated to acute asphyxia injury. It is important that birth asphyxia be defined precisely and distinctions made between primary and secondary asphyxia as these issues influence strategies for prevention and the exact contribution of asphyxia to long term outcome. Krishna and Sheriar (2000) acknowledge that although there have been great advances in our understanding of fetal and neonatal physiology and pathology related to perinatal asphyxia, there is a gap in the application of antenatal, intrapartum and neonatal interventions and management options.

New methods for fetal surveillance during labour are being investigated. They include continuous measurement of pH in fetal scalp tissue, fetal oxygen saturation with pulse oximetry and ECG waveform analysis (Jasper & Arulkumaran, 2000; Graham et al, 2008). The precise and early diagnosis of intrapartum asphyxia and hypoxic ischemia is critical, because there are therapies available, which if started early in the course of fetal hypoxia, may mitigate both its short and long-term effects (Perlman & Risser, 1996; Nordstrom & Arulkumaran, 2000). Among these therapies are pharmacological inhibitors of oxygen-free radicals, calcium channel blockers, timely delivery, brain cooling, seizure management and careful control of systemic blood pressure in the neonate. However, evidence from studies suggests that there is a very brief therapeutic window of time for intervention so early and accurate diagnosis of intrapartum asphyxia is crucial to outcome (Perlman, 2006). Abnormal fetal heart rate patterns, meconium staining of amniotic fluid and fetal acidosis may indeed be markers of fetal compromise but not necessarily compromise due to asphyxia. Currently, hypoxic ischemic encephalopathy is felt to be the best marker of an intrauterine asphyxial episode (ACOG, 2003).

2.6.6.1.6 Hypoxic ischemic encephalopathy as an indicator of asphyxia

Over the last 25 years, incremental knowledge has been gathered to describe better the role that acute hypoxic-ischemic injury may play in the origin of cerebral palsy (Speer & Hankins, 2003). Hypoxia refers to diminished oxygen in the tissues secondary to asphyxia (altered gas exchange) and ischemia refers to a deficiency in the flow of blood available for perfusion. Both of these can cause profound neurological damage when brain cells are affected. The type of neuronal necrosis resulting from hypoxic ischemia depends on the nature of the insult (acute or chronic), fetal condition before the asphyxia, vascular development, maturation of the brain and the effectiveness of resuscitation (Longo, 1997; McLean & Ferriero, 2004). Animal studies show that the duration
and degree of fetal hypoxia are related to the occurrence and extent of brain damage. The data in humans, however, are not as clear because the situation in humans does not allow experimental manipulation to determine the different factors involved. The timing and mechanism of brain-cell death might differ according to the mechanism, duration and intensity of the asphyxial assault as well as gestational age (Ferriero, 2004; Schifrin, 2004). Neuronal loss occurs in two phases, primary at the time of hypoxia/ischemia and the secondary during the re-oxygenation and re-perfusion period (Nordstrom & Arulkumaran, 2000; Verklan, 2008). The subsequent neurological manifestations reflect the location and distribution of the neuronal necrosis.

Substantial or prolonged intrapartum hypoxia sufficient to result in permanent neurological damage, essentially always produces manifestations of neurological dysfunction during the early days of life (Fenichel, 1983; McLean & Ferriero, 2004). This manifestation of neurological dysfunction is neonatal encephalopathy. Thus, the pathway from an intrapartum hypoxic-ischaemic injury to subsequent cerebral palsy must progress through neonatal encephalopathy (Badawi et al, 1998b; ACOG, 2003). Neonatal encephalopathy is currently advocated as the preferred term for describing the status of neurologically depressed newborns (ACOG, 2003; Wu et al, 2003).

2.6.6.2 Cerebral Palsy and Encephalopathy

Newborn encephalopathy is an important clinical problem associated with considerable morbidity and mortality and is central in the assignment of blame for causation of cerebral palsy in obstetric litigation (Badawi, 1998b; Miller, 2003). Studies have found that for term or near term babies, the strongest neonatal predictor of cerebral palsy is the presence and severity of encephalopathy (Nelson, 2002; Dixon et al, 2002). Neonatal encephalopathy and hypoxic ischemic encephalopathy are conditions defined in and described for term (>37 weeks gestation) and near term (34-37 weeks gestation) infants (ACOG, 2003). Neonatal encephalopathy is defined clinically based on a cluster of findings to include a combination of abnormal consciousness, tone, reflexes, feeding, respiration or seizures in the early days of life (Hankins, 2003; Volpe, 2008). The severity of encephalopathy is commonly classified as stage 1, 2 or 3 based on clinical symptoms set out by Sarnat and Sarnat (1976) or mild, moderate or severe according to criteria set out by Fenichel (1983).

The association between encephalopathy and cerebral palsy has often been taken mistakenly, to represent evidence of acute intrapartum asphyxia (Badawi et al, 2005; Fahy & King, 2005). Some infants with neonatal encephalopathy have neither recognized antepartum risk factors nor evidence of intrapartum hypoxia. Badawi et al (1998b) found that over 75% of cases of neonatal encephalopathy had no clinical signs of intrapartum hypoxia. Neonatal encephalopathy and its subset hypoxic ischemic encephalopathy can have multiple aetiologies other than intrapartum events, including nervous system anomalies, prenatal stroke, infection, drug exposure, trauma, cerebral malformation, metabolic disorders and genetic disorders (Nelson & Ellenberg, 1986; ACOG, 2003; Fahey & King, 2005). A Western Australian case control study by Badawi et al (1998a) looking at risk factors for neonatal encephalopathy among 164 infants (400 controls) found the independent risk factors for before conception and in the antepartum period to be;
socioeconomic status (Odds Ratio (OR) 3.6), family history of seizures (OR 2.55) or other neurological disease (OR 2.73), conception after infertility treatment (OR 4.43), maternal thyroid disease (OR 9.7), severe pre-eclampsia (OR 6.3), bleeding in pregnancy (OR 3.57), viral illness (OR 2.97), having an abnormal placenta (OR 2.07), intrauterine growth restriction (OR 38.2) and postmaturity (OR 13.2). The study concluded that 70% of cases of neonatal encephalopathy were probably caused by events arising before the onset of labour.

Badawi et al (1998b) found that the intrapartum risk factors for newborn encephalopathy include maternal pyrexia (OR 3.82), persistent occipitoposterior position (OR 4.29) and acute intrapartum events (OR 4.44). Operative vaginal delivery (OR 2.34) and emergency caesarean section (OR 2.17) were both associated with an increased risk. The results of the population based case-control study by Badawi et al (1998a, 1998b) suggest that the causes of newborn encephalopathy are heterogeneous and that many of the causal pathways resulting in newborn encephalopathy start before birth. A better understanding of these multiple pathways will be necessary in the diagnosis and prevention of newborn encephalopathy and hence cerebral palsy.

It should be acknowledged that infants with cerebral palsy frequently have not had neonatal encephalopathy and the presence of neonatal encephalopathy may or may not result in permanent neurological impairment. Badawi et al (2005) report that 3 quarters of the children born at term who developed cerebral palsy did not have a history of newborn encephalopathy. Studies looking at neuro-developmental outcome after neonatal encephalopathy have found that infants with mild encephalopathy have outcomes comparable to non-affected infants (Dixon et al, 2002; Van Handel et al, 2007). Those with severe encephalopathy will either die or invariably develop cerebral palsy or cognitive deficits (Robertson & Finner, 1993; Dilege et al, 2001; Pin et al, 2009; deVries & Jongmans, 2010). A systematic review of 13 empirical studies, looking at developmental outcomes following neonatal encephalopathy, conducted by Pin et al (2009) found adverse outcomes in none of the infants with mild neonatal encephalopathy, in 32% in those with moderate encephalopathy and in almost 100% of those with severe encephalopathy. The adverse outcomes examined included, death, cerebral palsy, cognitive impairment and sensory impairments. The authors acknowledge that they encountered significant heterogeneity between the studies relating to numbers of subjects, diagnostic criteria employed and outcomes examined.

Badawi et al (2005) subsequently followed up both case and control children from their study to the age of 5 years to determine their developmental outcome, including the presence of cerebral palsy. They report a neonatal case fatality rate of 9.1%. Thirteen percent of the children with newborn encephalopathy went on to develop cerebral palsy by the age of 5 years. Among their findings was that the severity of the encephalopathy was strongly associated with the subsequent risk of cerebral palsy. Cerebral palsy was diagnosed in 8% of the survivors of moderate encephalopathy and 23% of the survivors of severe encephalopathy. They also found that epilepsy was significantly more commonly associated with cerebral palsy following newborn encephalopathy (OR 2.7). Nelson (2005) has commented that the original 1998 study was and still is the only large
population-based investigation of multiple potential risk factors for hypoxic ischemic encephalopathy and the 2005 study provides valuable data on long-term outcome.

Badawi et al (2005) in their follow-up study conclude that nearly one out of every four children with cerebral palsy will be found on review to have evidence of encephalopathy in the newborn period. They do point out however, that this association between encephalopathy and cerebral palsy does not necessarily represent evidence of intrapartum asphyxia, as hypoxic ischemic encephalopathy is only one subgroup of newborn encephalopathy. Intrapartum hypoxia alone accounts for only a small proportion of neonatal encephalopathy. In their review of neonatal encephalopathy and cerebral palsy, ACOG (2003) concluded that the overall incidence of neonatal encephalopathy attributable to intrapartum hypoxia, in the absence of any other pre-conceptual or antepartum abnormalities, is estimated to be approximately 1.6 per 10,000 infants. When hypoxic ischemic encephalopathy is combined with neonatal encephalopathy from all other causes Badawi et al (1998a, 1998b, 2005) found the incidence to be 1.9-3.8 per 1,000. Following a systematic review (22 studies) of the role of intrapartum hypoxic-ischemia in the causation of neonatal encephalopathy, Graham et al (2008) concluded that in developed countries the incidence of hypoxic-ischemic encephalopathy at term was 2.5 per 1,000 live births and that the proportion of cases of cerebral palsy associated with intrapartum asphyxia was 14.5%. As with many similar studies, this systematic review by Graham et al was confounded by the use of numerous definitions for intrapartum hypoxic ischemia. Volpe (2008) suggests that approximately 20% of neonatal hypoxic-ischemic encephalopathy is related primarily to antepartum events including maternal conditions such as hypotension, placental vasculopathy and insulin dependent diabetes. He believes that intrapartum events such as prolapsed cord, abruption and traumatic birth are linked to 35% of hypoxic-ischemic encephalopathy cases, with conditions in the neonatal period (congenital heart disease, severe pulmonary disease) being responsible for as much as 10% of cases (Volpe, 2008). The disparity of findings in the various studies illustrate not just the heterogeneity of the study designs but the need for the standardisation of definitions around encephalopathy and its subset, hypoxic ischaemic encephalopathy. In any event, increasingly, the debate about the aetiology of perinatal brain injury and its contribution to the causation of cerebral palsy emphasises the relatively small contribution of the intrapartum period (Nelson & Ellenberg, 1986; Blair & Stanley, 1988; Badawi et al, 1998b; ACOG, 2003; Badawi et al, 2005).

Because we cannot directly measure intrapartum blood flow and oxygen delivery to the fetal brain, the specificity of the findings for intrapartum hypoxic-ischemia is unknown. The current markers of intrapartum compromise used to identify those infants during labour at greatest risk for developing hypoxic ischemic cerebral injury secondary to intrapartum asphyxia have limitations (Pharoah, 1995; Perlman, 1997; Low, 2004). It is known that the relationship between exposure to hypoxia and the outcome in terms of cerebral dysfunction is modulated by the individual infant’s vulnerability. The wide variability in the effect of hypoxic-ischemia on the newborn brain highlights the probability that various fetal, maternal and genetic factors play a significant modifying role in determining outcome. The markers currently at our disposal cannot identify accurately an asphyxial episode before birth nor can we determine the timing, duration or extent of those asphyxial
episodes. As fetal brain development and function cannot currently be visualised or monitored continuously, we also cannot currently assess the fetal adaptive mechanisms employed to preserve cerebral function during asphyxia episodes (McLean & Ferriero, 2004; Fahey & King, 2005; Ross 2011). However, the presence of neonatal encephalopathy and its neurological manifestations in the first days of life suggests the possibility of perinatal hypoxic-ischemia (Wu et al, 2006). Similar to the other measures traditionally considered to indicate damaging asphyxia (low Apgars, abnormal CTG, metabolic acidosis), encephalopathy, as a stand-alone tool is non-specific for diagnosing an acute intrapartum hypoxic event sufficient to cause cerebral palsy.

In an attempt to address the difficulties with identifying cases of cerebral palsy associated with intrapartum asphyxia, a multidisciplinary International Cerebral Palsy Task Force of scientists and clinicians working in this area was convened in 1997. The purpose of the task force was to define the current scientific evidence regarding the epidemiology, outcome and aetiology of neonatal encephalopathy and cerebral palsy (Speer & Hankins, 2003).

### 2.7 Cerebral Palsy and the Consensus Statement of the Cerebral Palsy Task Force

Between 1997 and 1998, an international task force of relevant specialists, experts and researchers called the International Cerebral Palsy Task Force, reviewed the literature on cerebral palsy. In an effort to better identify cases of cerebral palsy with neuropathology that began or became established around labour and birth, the International Cerebral Palsy Task Force (1999) published a consensus template for defining a causal relation between acute intrapartum events and cerebral palsy (MacLennan, 1999). The template set out objective criteria necessary to define in retrospect that an acute intrapartum hypoxic event had occurred before the onset of cerebral palsy. This group defined essential criteria that list clinical and biochemical markers that define an acute intrapartum event. The consensus was that these are the criteria that should be met before attributing cerebral palsy to an intrapartum hypoxic event. The task force recommend that to attribute cerebral palsy to intrapartum hypoxia one must have both the absence of other demonstrable causes and the presence of the sequence of clinical markers set out in the objective criteria. The template has more recently been updated, slightly modified and endorsed by the Neonatal Encephalopathy and Cerebral Palsy Task Force and a report to that effect was published in 2003 by the American College of Obstetricians and Gynaecologists (ACOG).

The template (Table 2.1) describes 9 criteria to be sought to define an acute intrapartum hypoxic event sufficient to cause cerebral palsy; four essential criteria which help identify the existence of severe hypoxia at birth and 5 criteria that if present together suggest intrapartum timing, but by themselves are nonspecific to asphyxial insults. All four of the essential criteria must be met before an intrapartum hypoxic cause can be considered. At least 3 of the additional suggestive 5 criteria have to be present to suggest a possible acute event rather than longer-standing hypoxia or other chronic pathology (Strijbis et al, 2006). The authors suggest that the use of these criteria to define an acute intrapartum hypoxic event sufficient to cause cerebral palsy will help to evaluate the probability that the pathology causing the cerebral palsy occurred during labour. They also suggest
that when applied properly, the template will help exclude non-hypoxic and chronic hypoxic causes of cerebral palsy (MacLennan and Robinson, 2004).

Table 2.1: Criteria to Define an Acute Intrapartum Event Sufficient to cause Cerebral Palsy

<table>
<thead>
<tr>
<th>Essential Criteria</th>
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<tbody>
<tr>
<td>1. pH &lt; 7.00 and base deficit ≥ 12 mmol/L</td>
</tr>
<tr>
<td>2. Onset of neonatal encephalopathy within 24 hours</td>
</tr>
<tr>
<td>3. CP of the spastic quadriplegic or dyskinetic type</td>
</tr>
<tr>
<td>4. Exclusion of other pathologies associated with CP</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Suggestive but non-specific to asphyxia insults</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Sentinel hypoxic event</td>
</tr>
<tr>
<td>2. Sudden sustained fetal bradycardia or other evidence of non-reassuring fetal status</td>
</tr>
<tr>
<td>3. Apgar scores of 0-3 beyond 5 minutes</td>
</tr>
<tr>
<td>4. Multisystem failure within 72 hours of birth</td>
</tr>
<tr>
<td>5. Evidence of acute non-focal cerebral abnormality on early imaging</td>
</tr>
</tbody>
</table>

Although the 2003 ACOG template has been described as the most extensively peer-reviewed document on this complex subject published to-date (Hankins & Speer, 2003), it is not immune to criticism. The main thrust of the template has been challenged in the literature and has failed to achieve widespread acceptance beyond the obstetric community. The overall scientific validity of the review is the subject of dispute. The document itself does not describe the method of data analysis employed. The authors state that the document has a reasonable scientific basis and can be referenced but they do not elaborate any further. The process undertaken to arrive at the consensus statement did not include a meta-analysis or systematic review of the literature.

Many experts have rejected the strict criteria within the template. Some commentators have expressed uncertainty regarding how discriminating the agreed criteria really are (Dear & Newell, 2000; Rosenbloom & Rennie, 2000). Schifrin (2004) contends that devising a set of clinical criteria that will distinguish clearly between babies who have experienced intrapartum asphyxial injury and those who have not appears insurmountable using the criterion detailed in the template. He argues that more relevant dynamic tests of injury, such as neuroradiological studies and rigorous cardiotocograph interpretation, are necessary. Schifrin and Ater (2006) argue that numerous pitfalls await those who attempt to define the severity of intrapartum asphyxia or the risk of subsequent injury based on an umbilical pH or other ‘essential criteria’ suggested by various authoritative guidelines. Although there is a lack of consensus regarding the reliability of the various different criteria, the ACOG task force contend that it is the combination of high-risk markers in the essential criteria that make the template useful, rather than each single marker.

Strijbis et al (2006) attempted to apply the objective criteria retrospectively in a cohort of cerebral palsy cases. They found that the objective criteria set out in the consensus statement did not define that the acute hypoxic event was the primary cause of the cerebral palsy but rather it defined the few cases of cerebral palsy that might have been associated with acute intrapartum hypoxia. Korst
et al (1999) described cases in which it was clear that the newborn had experienced an acute intrapartum event such as uterine rupture or a prolapsed cord yet only one met the ACOG criteria for intrapartum hypoxia. Critics also predict that information about the essential criteria will be frequently missing from the medical records (Greenwood et al, 2003).

The authors of the 2003 consensus statement hoped that it could be used to provide a more objective criterion when discussing causation in clinical negligence litigation. Significant medico-legal question arise in cerebral palsy cases because of persisting difficulty with deciding whether a brain injury was sustained during labour and birth or before the onset of labour and whether or not it was preventable. However, Perlman (1997:855) argues that the inability to accurately assess prospectively the fetal adaptive mechanisms to maintain cerebral perfusion during episodes of asphyxia and the inherent tolerance of the fetal brain to intrapartum asphyxia using current markers renders it almost impossible with any degree of certainty, to offer legal opinion as to whether an alternative clinical strategy could have altered the neurological outcome or whether the outcome was unavoidable. Legal commentators have questioned the reliability of the template in clinical negligence litigation and the motivation behind it.

Criticism from the legal community has been severe. Reis (2004) accuse the authors of self-interest and lack of objectivity. He suggests that the intent of the ACOG was to reduce the burden of litigation on obstetricians and paediatricians. Pickering (2000:143) accuses the task force of adopting defence overtones designed to limit the exposure of healthcare providers to clinical negligence claims. Pickering’s argument is that by advocating absolute certainty through an insistence on set criteria, the template attempts to exercise a judicial function despite the fact that absolute certainty is not the legal standard to satisfy burden of proof in legal tests of causation. The legal test of causation is based upon the balance of probability not absolute certainty. Cunningham (2003) condemns the ACOG template as a corruption of the medical literature with articles designed to protect doctors in court. On the other hand, the medical community seem to suggest that the legal community may also have a vested interest. Freeman (2009) in commenting on the need to examine cerebral palsy clinical litigation argues that trial lawyers will undoubtedly oppose elimination of the right to sue for damages caused by medical negligence. The suggestion being that cerebral palsy litigation is very lucrative for the legal community and thus the legal fraternity will not welcome any developments that may reduce the amount of income generated by their work in this area. Although not universally accepted, the authors of the 2003 template argue that it provides a more objective criterion in medico-legal cases than expert opinion. The ACOG (2003) proposed that the multidisciplinary review and resulting template may help those who offer expert opinion when counselling in this area or giving such opinion in court.

2.8 Cerebral Palsy and Clinical Negligence Litigation

The debate about litigation in obstetrics and midwifery has focused largely on the issue of cerebral palsy (Symon, 2002). Although cerebral palsy is not known to be preventable by means now available, lawsuits brought against obstetricians and midwives for not preventing its development are a major contributor to the high cost of clinical litigation (Nelson, 2003; Sartwelle, 2009).
Advances in medicine have led to a public expectation that we should be able to prevent cerebral palsy. The public view is that modern reproductive research eliminated all the risks and hazards associated with childbirth, therefore only perfectly healthy babies are accepted in society today (Herczeg, 1997; Lupton, 1999; Symon, 2002). Safe childbirth is seen in modern society as a right and has become an absolute expectation in most developed countries (Symon, 2006; Sartwelle, 2009). Practitioners involved in maternity care have found themselves increasingly the subjects of complaints and legal claims as the expectations of the public have increased. If a baby is born with a neurological defect, the parents may feel that someone responsible should be found. Some parents of disabled children resort to civil court action seeking damages for alleged negligence around the time of birth. These actions are often based on the belief that in every case of a bad outcome, someone must have done something wrong. The unfavourable outcome is regarded as a consequence of a negligent act (Herczeg, 1997; Lupton, 1999). Following years of convincing the public that healthy newborns are the result of hospital based care provided by obstetricians and midwives; it is perhaps unsurprising that that same public then intuitively believe that a less than healthy baby is the obstetrician’s, midwives’ or hospital’s fault (Sartwelle, 2009). Despite the fact that the presence of cerebral palsy does not always imply human error or clinical negligence, our increasingly litigious society constantly seeks compensation for injury, whether there is fault to the injury or not. There are very significant costs involved in raising a child with cerebral palsy and this may play a role in the decision by parents to pursue legal action. With no guarantee from the State to cover the child’s healthcare and living costs, parents may feel they have no alternative but to recover costs of care through litigation. Legal actions are soaring and reaching an unbelievable number in developed countries.

The unprecedented rise in maternity care litigation is a growing problem in Western countries and its escalating costs, together with the increase of medical malpractice insurance premiums, is a major concern for maternity service providers (Meadows, 2000; Blumenthal, 2001; Ferryman, 2001; Williams & Arulkumaran, 2004; Wheat 2005). Medical liability for obstetricians and hospitals continues to be a major cost paid by insurance providers. There are suggestions in the American literature that liability insurance costs may have forced many providers of obstetric care to withdraw their services (Darr, 2004; MacLennan et al, 2005; Clark et al, 2008). In the United States, obstetricians have an average of 2.6 claims filed against them during their careers, 61% of which are obstetrics-related, the majority for allegedly birth-related cerebral palsy (Hankins et al, 2006). The UK National Audit Office (2001) estimated that cerebral palsy and brain damage cases accounted for 80% of the value of all legal claims in the UK. Litigation arising from the Irish maternity services accounts for approximately 25% of the number of cases reported to the Clinical Indemnity Scheme (CIS) and 60% of the value of claims (State Claims Agency, 2010). In Ireland, the Clinical Indemnity Scheme (CIS) was established in 2002 in order to rationalise pre-existing medical indemnity arrangements by transferring to the state responsibility for managing clinical negligence claims and associated risks. Under the scheme, which is managed by the State Claims Agency, the state assumes full responsibility for the indemnification and management of all clinical negligence claims, including those that are birth related. The State Claims Agency maintains a
database containing reliable, accurate data about the number of claims for damages, the success or failure of those claims, the amounts paid as well as demographic and clinical information about the children with cerebral palsy. Analysis of the State Claims Agency data could explore the distribution and characteristics of clinical negligence claims among cerebral palsy cases in Ireland as well as establishing the distribution of intrapartum injuries in the clinical negligence cases. Antoniotti (2011:44) contends that the CIS was required because of the fact that the commercial insurance market had reached a point whereby it was no longer willing to provide insurance cover to obstetricians or to hospitals with obstetric units due to the escalation in the size of Court awards and costs in cases of birth injury.

The main reason for this high total sum paid out is because claims relating to cerebral palsy and hypoxic brain injuries involve very large settlements. These settlements are guided by precedent and regularly exceed €3 million (Blumenthal, 2001; The Irish Times, 2009). Such large settlements reflect the projected costs of providing for a profoundly damaged child for their entire life. These costs are based on life expectancies that are increasing with improvements in care and in many cases need to cover the costs of nursing care. The high sums also reflect the cost of suitable housing and its adaptation as well as sophisticated equipment, aids, appliances and assistive technology now available to improve quality of life. In practical terms, the explosion in litigation means that there is a danger that large proportions of health care funds are being channelled into settlements rather than care.

The current Irish system of clinical negligence litigation is fault-based and involves adversarial lawyers who hire their own experts. The purpose of this common-law system is to compensate those who are injured by negligent care for the costs of care, and to pay compensatory damages for pain and suffering. The ever-increasing number of maternity care legal claims, concerning cerebral palsy, usually relate to alleged negligence in the intrapartum period. The crucial first step for a successful legal action is to establish that damage has occurred. It is usually evident in a cerebral palsy case that damage, in the form of a brain injury, has occurred. Causation refers to the question as to whether the action (or failure to act) of the practitioner was the cause of the damage (Symon, 1998a; Griffith, 2008). To establish negligence, a direct causal link between the breach of a duty of care and the ensuing damage must be established (Symon, 1998a; Symon, 2002; Griffith, 2008). The causal connection is crucial within a fault-based system. Causation has become an especially fierce battleground in medical negligence law (Reis, 2004; Williams & Arulkumaran, 2004). When establishing causation in cerebral palsy cases, the question to consider is whether brain injury is a direct consequence of actions or failure to act on the part of care providers. Once cerebral damage is diagnosed the focus shifts to the question of liability. Liability refers to the determination of whether or not the standard of care fell short of acceptable practice and whether or not appropriate action was taken (Symon, 1998a; Griffith, 2008). Liability and the standard of care is usually judged on what a reasonably competent practitioner would have done, known as the Bolam Test in the UK and the Dunne Test in Ireland (Mills, 2002). Expert opinion is usually sought to determine what the ordinary competent practitioner would be expected to do. This expert opinion may be challenged by the opposing expert opinion. For a claim to succeed it has to be established,
on the balance of probabilities, that the damage could have been avoided but for the negligence in care (Symon, 2002). If a breach in the standard of care is established then compensation may be awarded. Cases may also be settled with no admission of liability by the care provider.

There are growing attempts by health service providers to curb the spiralling costs of obstetric litigation (Williams & Arulkumaran, 2004; Studdert et al, 2006). There has been considerable discussion of possible alternatives and options for reform to the current system which is recognised to be overly adversarial, too lengthy and too costly (Quill, 1999; Symon, 1999a; Diamond, 2001; Mason & McCall Smith, 2000). There are many advocates for a ‘no-fault scheme’ where compensation payments would be made on a no-fault basis without recourse to litigation. However, there have been some arguments that such a scheme would prove very expensive and fails to address poor standards of care (Symon, 1999c). A redress scheme with fixed tariffs has been suggested (Diamond, 2001). Other possible reforms suggested are to phase out lump sum damages and introduce structured or phased settlements. Such a system of periodic payment orders has been in place in the UK for a number of years. An Irish working group on medical negligence and periodic payments has presented a report on its deliberations, around periodic payments, to the High court for consideration (Quirke, 2010). The group are currently working on module 2 of their deliberations that concern the case management of medical negligence cases. There are also advocates for mediation as an alternative to formal litigation.

Freeman (2009), an American commentator, argues that trial lawyers will undoubtedly oppose elimination of the right to sue for damages caused by medical negligence, as they will view this approach as a threat to their substantial incomes. Freeman (2009) goes on to suggest that the lawyers are well compensated with a large percentage of the award despite the fact that most people believe that the award is going to the damaged child. According to the Irish clinical indemnity scheme, for each euro of compensation paid to claimants in negligence cases, the CIS pay an additional 56 cent in legal costs (Breen, 2008). There have also been recommendations to establish special courts for clinical negligence cases presided over by judges with particular expertise in the area (Hankins et al, 2006; Freeman, 2008). Criticisms of the current courts are that the courts in which these cases are adjudicated have judges who do not have particular expertise in this area (Freeman, 2009). Symon (1999b) advocates moves to establish lists of expert witnesses for these special courts in an attempt to simplify the legal process and to minimise delays in obtaining expert reports. In cases of adverse perinatal outcome, reasons for litigation often originate from parents frustration with seeking a satisfactory explanation of how their baby was injured and why (Herczeg, 1997; Symon, 2002). Modern, clinical risk management guidelines advocate organisational openness and transparency with regard to giving explanations and apologies as a way of avoiding people seeking redress in the Courts. This is referred to in the literature as open disclosure and is currently receiving some attention in the Irish context (Breen, 2009).

Although cerebral palsy is not known to be preventable by means now available, legal action brought against obstetricians and midwives for not preventing such outcomes are a major
contributor to the high cost of clinical litigation (Nelson, 2003; Sartwelle, 2009). The evidence linking brain damage to intrapartum care remains uncertain but this has become the dominant litigation theme internationally (Young et al, 2001). Establishing a link between intrapartum events and cerebral palsy remains problematic; nevertheless, many people seem prepared to assume such a link (Symon, 1998b; Clements, 2001; Nelson, 2003). This is because there is a widespread perception that adverse events in labour are usually potentially preventable, whereas cerebral palsy arising in the antenatal period is considered largely non-preventable (Greenwood et al, 2003). The relation between quality of care that is given to a mother during labour and birth and cerebral palsy in a surviving child is a continuing source of debate involving obstetricians, midwives, paediatricians, parents and the legal profession (Simpson & Knox, 2000).

In the courts, much of the debate about clinical negligence around birth injuries focuses on whether or not there is evidence of acute intrapartum hypoxia and if so whether the care provided was negligent (Simpson & Knox, 2000). The belief persists that intrapartum hypoxia is preventable, and therefore someone’s fault. This is despite the findings of multiple epidemiological studies, that intrapartum hypoxia can be secondary to a number of antenatal conditions such as neonatal stroke or cystic periventricular leukomalacia, which have no relationship to negligent care. Even with the best care, not all potentially damaging intrapartum events are avoidable (Badawi et al, 1998b). Despite this, many cases continue to be attributed to negligent care during labour and birth, therefore, better ways of identifying timing of brain insults are needed (SCPE, 2000). The challenge for practitioners is to differentiate between potentially avoidable intrapartum events and those events over which we seem to have no control. This has focused many studies on discriminating whether brain injury is related to antepartum and/or intrapartum asphyxia (Perlman, 1997). In an attempt to address some elements of this uncertainty the authors of the ACOG cerebral palsy consensus statement (2003) hoped that expert witnesses as well as Claimant and Defendant legal advisors might adopt the statements defined criteria when offering legal opinion and assessing liability. The authors hoped that the consensus statement would provide an agreed reference for use by the courts. They believe that the clarity provided by the statement could lead to a different approach to decision making in the legal system (ACOG, 2003). However, the statement has not become widely utilised by either, the medical, midwifery or legal profession.

2.9 Discussion and conclusion
Cerebral palsy is a complex condition, about which knowledge and understanding has grown substantially over the last number of decades. Considerable epidemiological evidence supports the view that cerebral palsy is heterogeneous in both its manifestations and its causation. Research has focused on identifying factors that are associated with an increased risk of cerebral palsy. Unfortunately, studies have found that there are relatively few specific, modifiable risk factors for cerebral palsy and this makes prevention very difficult. Intervention has focused on avoiding exposure to the known associated risk factors. Regrettably, this approach has failed to provide evidence of preventability of the disorder; such is the complexity of the condition. Advances in maternal-fetal medicine in recent years, has not seen a reduction in the prevalence of cerebral
palsy. Interventions that are aimed at preventing cerebral palsy as a consequence of adverse events during labour, such as electronic fetal monitoring and caesarean section, have not been shown to have achieved the goal of contributing to a reduction in cerebral palsy. The human and financial costs of cerebral palsy remain extremely high and allegations of preventable intrapartum hypoxia resulting in cerebral palsy continue to contribute significantly to clinical negligence litigation.

Despite decades of worldwide research indicating that only a very small proportion of children with cerebral palsy have had an intrapartum hypoxic event (Nelson et al, 1986; Blair and Stanley, 1988; Gaffney et al, 1994; Sartwelle, 2009) the inadequacy of markers of perinatal hypoxia result in continuing uncertainty and confusion in this area (Blair, 1993; SCPE, 2000). This uncertainty has precipitated many studies attempting to discriminate whether brain injury is related to hypoxia and establishing the timing of that brain injury. In an attempt to address some elements of the uncertainty, the ACOG (2003) task force proposed a set of objective criteria to define in retrospect that an acute intrapartum hypoxic event had occurred before the onset of cerebral palsy. Robust studies are needed to test the use of the consensus statement and the applicability of the ACOG criteria in clinical practice. Continuing research is imperative to provide greater understanding about the origins of cerebral palsy and the small part played by intrapartum hypoxia in causation. The following research study will apply the ACOG criteria for the identification of acute intrapartum hypoxia in practice and so test the utility of the consensus statement. The study will also describe the various antenatal, intrapartum and neonatal factors associated with cerebral palsy in a cohort of children. The following chapter outlines the overall research process used in achieving these objectives of the study.
Chapter 3
Methods

3.1 Introduction
The aim of this study was to apply objective criteria for the identification of acute intrapartum hypoxia in a cohort of children with cerebral palsy and to describe other cerebral palsy related factors in the cohort. This chapter outlines the overall research process used in achieving the aim of the study. The research process was informed by Cotty's (1998) four elements framework for the social research process. This chapter presents details of the study approach by describing the research methodology, the sampling strategies utilised, the development of the data collection instrument and its reliability and validity evaluation, the procedures for data collection and analysis and the ethical considerations of the study.

3.2 Aim of the study
This study will describe the prevalence, distribution and interrelationships of antenatal, intrapartum and neonatal variables associated with cerebral palsy and apply the objective criteria for the identification of acute intrapartum hypoxia in a cohort of children with cerebral palsy.

3.3 Objectives of the study

- To report the distribution of antenatal, intrapartum and neonatal factors associated with cerebral palsy in the cohort;

- To identify the availability of data in the maternal and neonatal records to facilitate application of the essential criteria for defining a causal relation between acute intrapartum events and cerebral palsy put forward by the Neonatal Encephalopathy and Cerebral Palsy Task Force Report (ACOG, 2003);

- To apply the ACOG (2003) criteria for defining acute intrapartum hypoxia in the cerebral palsy cohort.

3.4 Research Process
The overall research process in this study was informed by Crotty's (1998) four elements framework for the social research process. Crotty (1998) contends that describing the research process establishes the credentials of the study by setting out clearly the processes engaged in during the conduct of the research and clearly articulating its theoretical underpinnings. The use of Crotty's framework enabled the researcher to apply a systematic, coherent and logical organising structure to guide the study. Crotty's framework facilitated the concrete identification of the somewhat abstract theoretical concepts described in the literature and thus gave clarity to the description of the research process. The four elements of Crotty's framework are identified as;
epistemology, theoretical perspective, methodology and methods and are synonymous with objectivism, positivism, cohort study and quantitative data collection in this study. The epistemology, theoretical perspective and methodology are sometimes referred to in the literature as the overall research paradigm informing the methods used.

3.4.1 Epistemology

Epistemology refers to the philosophy of knowledge or, how we know what we know about the world around us. Differing epistemological beliefs centre on the question of whether there is one reality or multiple realities and how we come to know those realities. In this study, the philosophy of knowledge underpinning the conduct of the research was objectivism. Objectivist epistemology relies on deductive reasoning to establish theory that can be tested. Objectivism is a view that things exist as meaningful entities independently of consciousness and experience, that they have truth and meaning residing in them as objects (Crotty, 1998:5). In order to meet the aims and objectives of this study the researcher wished to collect information essentially related to the prevalence and distribution of variables associated with cerebral palsy among a specific cohort. The researcher needed to gather data from medical records and examine that data as objective, bias-free facts in a deductive manner. Hence, deductive reasoning underpinned by an objectivist epistemology guided the collection and interpretation of data for this study.

3.4.2 Theoretical perspective

The theoretical perspective refers to the philosophical assumptions held by individuals about the nature of reality. In other words, the different ways people view the world. Thus, in the context of a research study, the underlying philosophical assumptions of the researcher influence how phenomena are researched. The philosophical stance is determined partly by the nature of the research question and partly by the researcher’s philosophies and assumptions about the world and the nature of knowledge (Collis and Hussey, 2003). The theoretical perspective informing the research methodology and the choice of methods for this study is positivism. Positivism is rooted in 19th century thought, guided by such philosophers as Compte, Newton and Locke and reflects an emphasis on the rational and scientific (Polit & Beck, 2006; Burns & Grove, 2009). Positivists believe that an objective reality exists independent of human observation as opposed to the constructivist view that knowledge is established through the meanings attached to the phenomena studied. Krauss (2005) suggests that positivists believe that data and their analysis are value free and that data do not change because they are being observed. This was certainly the case for this study in that the data already existed as value free items in the medical records and did not change in any way through being observed by the researcher.

Positivism is often criticised as being reductionist, preoccupied with quantification and thus limited in its nature and so inconsistent with the holistic nature of nursing and midwifery (Letourneau & Allen, 1999; Krauss, 2005; Weaver & Olson, 2006). In recent times philosophers like Popper (1902-1994) Kuhn (1922-1996) and Feyerabend (1924-1994) have argued that positivism is not suited to
modern science. A new philosophy, post-positivism, that acknowledges the need for multiple theories and methods is emerging. In adopting a positivist perspective, this researcher does not deny the importance of the subjective, social and spiritual aspects of the experiences of people living with cerebral palsy. Neither does the researcher deny the human uniqueness and complexity of each cerebral palsy sufferer's experience. Rather, the researcher made a pragmatic commitment to what actually works in practice for achieving the specific aim of this particular study. The strengths and weaknesses of various approaches to addressing the research aims were considered and justifiable options were then selected. The aim of the study was to apply a set of objective criteria to the phenomenon under study and this was congruent with the positivist perspective. Thus, the positivist theoretical perspective underpinning the goals of this study guided the objective observation, measurement and description of the phenomena under study. Those phenomena were cerebral palsy and its associated factors.

It is, of course, also possible that inherent positivist ontological and epistemological assumptions held by the researcher had implications for the choice of aspects of cerebral palsy chosen to explore, for the choice of questions asked and for the choice of approach subsequently used to conduct the study. It could be argued that the underlying (positivist) philosophical assumptions held by the researcher about the nature of reality and the nature of knowledge was what led the researcher, after an extensive literature review to choose to examine an essentially ‘quantitative’ aspect of cerebral palsy as opposed to an essentially ‘qualitative’ aspect. In any event, positivism as a theoretical perspective informed the research methodology and the choice of methods used for this study.

3.4.3 Methodology

The research methodology refers to the strategy or approach adopted for the study. The methodology chosen depends on what the study aims to achieve as well as the philosophical orientations that inform the values and beliefs of the researcher and which in turn, inform the overall conduct of the study. As there is a paucity of uniquely Irish data in both the national and international cerebral palsy literature, this study was undertaken to provide a comprehensive picture of cerebral palsy in Ireland. Pragmatic decisions around the methodology employed for this study were made by the researcher based on the aim of the study, the available resources, including human, financial and time resources and based on how accessible the participants were. According to Burns & Grove (2001) the methodology guides the researcher in planning and implementing the study in a way that is most likely to achieve the intended aims and objectives. Thus, an epidemiological approach using an observational methodology was adopted for this study to enable the observation and description of cerebral palsy and its associated factors.

Epidemiology

From a nursing and midwifery perspective, it is acknowledged that Florence Nightingale applied epidemiological principles to identifying the causation of ill health in British soldiers (Whitehead, 2000). Although there is a long-standing tradition of epidemiology in health care (Spruit & Kromhout, 1987), epidemiological study has been traditionally viewed as the domain of medicine.
rather than that of nursing and midwifery. Searching the literature revealed very little evidence of epidemiological activity in nursing research and even less in midwifery. Epidemiological research is central to the commissioning of healthcare and the formulation and implementation of national, regional and local health policy (Moon et al, 2000; Whitehead, 2000). Epidemiology provides the evidence for health policy. Thus, nurses and midwives need an epidemiological knowledge base if they are to play an active part in determining, planning and implementing person-centred, evidence-based health policy (Antrobus & Kitson, 1999; Crossan, 2003; Davies, 2004).

Epidemiology provides a key approach to understanding health and disease in individuals and populations, and the forces and factors that influence them. Epidemiological research is used to quantify risks by examining correlations between ‘risk factors’ and outcomes. Such correlations may be evidence of, but are not proof of, causation. Epidemiological studies seek to establish if there are associations between risk factors (exposure) and disease (or other outcome) so that preventative measures can be taken to limit the morbidity and mortality of the disease (Bailey et al, 2005). Epidemiological researchers collect information concerning constructs such as mortality and morbidity, occurrence of disease, population distribution, the natural history or progression of diseases and the relationships between diseases and their associated factors and risks (Spruit & Kromhout, 1987; Mulhall, 1996). This makes it a particularly suitable type of enquiry for exploring cerebral palsy and its associated factors. While such data can tell us which kinds of babies are most likely to experience cerebral palsy, they cannot tell us whether a particular individual will experience that cerebral palsy or not.

**Observational Studies**

Areas of epidemiological research are not generally amenable to investigation through randomised trials. Therefore, non-experimental, observational studies are often used by epidemiologists. Observational studies collect information about a group of subjects but do nothing to affect them. These studies are non-experimental because the researcher does not manipulate the variables. In observational studies, data are obtained in a systematic manner that enables the researcher to describe phenomena and to investigate relationships or differences among variables. Although observational studies can provide information about associations between variables, they cannot determine whether those associations are causal or not (Polit & Beck, 2008). However, inferences are made about causation in observational studies by measuring the strengths of associations and the consistency of associations across a range of studies (Webb et al, 2005; Cluett & Bluff, 2006). Descriptive observational studies are often considered to be one of the weaker methodologies in the research hierarchy, with randomised controlled trials considered to be the strongest (Vandenbroucke, 2008; Lu, 2009). Observational studies are non-experimental and this increases the potential margin of error due to residual confounding and inherent biases.

Notwithstanding their limitations, observational studies are necessary to describe the frequency, natural history and possible determinants of a condition (Grimes & Schulz, 2002). It is widely recognised that the results of these observational studies often generate hypotheses that can be examined through further analytical studies (Grimes & Schulz, 2002; Szklo & Nieto, 2007;
Vandenbroucke, 2008). It is true that observational studies are unable to determine causal relationships between exposures and outcomes; however, they can produce inferences about cause for further study. Due to its position in the traditional research hierarchy, the findings from observational studies are sometimes considered to be less reliable than those with an experimental design (Vandenbroucke, 2008; Lu, 2009). Good study design and data analysis are critical in observational studies to address these concerns about the validity of evidence and to ensure credible results. While not advocating uncritical acceptance of all observational research, the legitimacy of the findings produced by robust observational studies must be acknowledged. Despite the methodological constraints of observational research it does represent the best available approach for the achievement of the aims and objectives of this particular study into cerebral palsy.

**Cohort Study**

There are two main types of observational studies; case-control study and cohort-study. In a cohort study a group of participants, who have similar characteristics or who have experienced a particular event is identified and studied (Burns & Grove, 2001). For this research project, a cohort study was conducted within a geographically defined cohort of children whose characteristic of similarity was a diagnosis of cerebral palsy. A retrospective design was employed as the sample and the outcome already existed and the study aimed to collect data about factors believed to be related to that outcome in a given sample. The retrospective design allowed the examination of a wide range of exposure and outcome data that were readily available in medical records and on the cerebral palsy register. As this study was undertaken as a PhD project, the time and budget restraints meant that a prospective design would not have been appropriate as it would have involved the need for follow-up over many years to get data on outcome. The cohort study methodology adopted for this research was advantageous for a number of reasons. The study methodology enabled the description of the cohort, the identification of related factors associated with cerebral palsy and the collection of information in a systematic and accurate manner to meet the aims and objectives of the study. The cohort methodology chosen, directed the selection of the population, the sampling procedure, the methods of measurement and the plan for data collection and analysis for this epidemiological study.

### 3.4.4 Research Methods

The research method refers to the processes and techniques used by the researcher to conduct the study. As is usually the case for studies in the positivist paradigm, quantitative research methods were employed for this study. The quantitative approach provides hard, objective facts that can be measured, described and interpreted and can focus on how particular factors are distributed in a population (Parahoo, 1997; Gerrish & Lacey, 2006). Thus, quantitative methods were ideally suited to this epidemiological study. Quantitative data were collected retrospectively from maternal and neonatal records using a specifically designed data extraction form. The variables selected by the data extraction form were congruent with the quantitative methods employed. The data extraction form was designed to ensure that precision, objectivity and rigour were applied to the collection of data. Collies and Hussey (2003) advocate this approach as
helping the researcher to remain distant when conducting their research and not allowing values and bias to distort the objective view. Objectivity was particularly relevant for this study as the researcher was the sole researcher and designed the data extraction instrument, administered it and analysed the data herself. This is recognised as a potential limitation of the study.

3.5 Population and Sample Selection

The target population of interest in this particular study are children with cerebral palsy and the subset for sampling are a cohort of cerebral palsy children registered on the West of Ireland Cerebral Palsy Register (WICPR). A population is the aggregate of entities in which a researcher is interested. Sampling is the process of selecting a subset of that population for research (Polit and Beck, 2006). There are two broad types of sampling designs in quantitative research: probability sampling and non-probability sampling (Parahoo, 1997). Probability sampling is used when a specific, predefined group is needed to meet a study’s aims and objectives. As this study needed to target a sample population with a known experience; children in the West of Ireland with cerebral palsy, this researcher used non-probability (purposive) sampling. Non-probability sampling enables the selection of cases that are particularly informative and best answer the research question to meet the research objectives (Saunders et al, 2003).

It is known that non-probability sampling of the target population may lead to non-representative sampling of the population subset (Burns & Grove, 2001). Nonetheless, the non-probability sample chosen for this study represents the cerebral palsy population of the West of Ireland. This means that although the results of the study may not be generalisable to the entire population of children with cerebral palsy, the associations found are valid and applicable to the restricted sample of the West of Ireland (McNeil, 1996). The researcher therefore is limited by the sampling method to generalising the findings to the West of Ireland sample. Consideration will be given to this when analysing the data. There is scope to conduct similar studies with comparable cohorts on the other cerebral palsy registers in Ireland in the future.

According to Cluett & Bluff (2006) availability of and access to potential participants will also influence the sampling method chosen. There are other cerebral palsy databases in the country but the WICPR was the one to which this researcher had access, thus the non-probability sample targeted were children on the WICPR. The overall sampling process involved identifying the population of interest, specifying the eligibility criteria and accessing and recruiting the study participants (Polit and Beck, 2006).

3.5.1 Inclusion and exclusion criteria

Having identified the sampling frame as children with cerebral palsy in the West of Ireland, inclusion and exclusion criteria were then specified to develop the desired sample. Inclusion and exclusion criteria list the characteristics essential for membership to a study sample (Burns & Grove, 2001). To be eligible to participate in this observational study the participants must be
children and mothers included on the WICPR who have given consent for their data to be accessed. Children with cerebral palsy in the West of Ireland who were not registered on the WICPR were excluded. Children on the WICPR who had subsequently died (n=7) were also excluded as it was felt that in the absence of any relationship with the researcher, parents may have been offended and upset by an approach. Children who were registered on the WICPR and still alive but from whom consent was not received were not included. Inclusions and exclusions criteria ensure internal validity, acknowledging that generalisability of the findings (external validity) will be limited to individuals similar to those studied (Brink & Wood, 1998).

3.5.2 Access to potential participants

Permission to carry out the study was obtained in writing from the relevant local HSE ethics committees (Appendix 3.1) concerning each of the relevant maternity units. Permission was also obtained from the Faculty of Health Science, National University of Ireland, Galway Ethics Committee (Appendix 3.2).

3.5.3 Recruiting participants

Recruitment of the sample involved accessing the WICPR database. Children with cerebral palsy in the West of Ireland have information about them entered on a database called the West of Ireland Cerebral Palsy Register (WICPR). Children are registered on this database at 5 years of age with parental consent. The register is managed by a data controller. The researcher needed contact details for the children on the register to request their consent to access their records. The data controller was enabled to provide those contact details to the researcher as the initial consent given by parents to register the children on the database allows their information to be used in further studies. The data protection commissioner (2007) recommends that if the researcher is not an employee of the data controller, an appropriate data controller to data processor contract needs to be put in place stipulating the duty of confidentiality that the researcher owes to the participants. This appropriate contract takes the form of a ‘data confidentiality agreement’ and a ‘data agent nomination form’. As this researcher is not an employee of the data controller, both these recommended forms were signed by the researcher and the data controller for this study, to further enhance the protection of the privacy and confidentiality of the recruited participants (Appendix 3.3 & 3.4).

All 129 living children registered on the WICPR were invited to participate in the study. The written invitation to participate in the study was distributed by post in April 2010 (Appendix 3.5, 3.9). Curtis and Redmond (2009) suggest that the timing of the invitation should consider seasonality. They recommend that researchers should avoid approaching potential participants during significant holidays and just before Christmas. Therefore, the letters of invitation were posted in late April to avoid the summer and Easter holidays.
3.5.4 Sample size

The number of participants in a sample is a major issue in conducting and evaluating quantitative research (Playle, 2000; Polit & Beck, 2006). Quantitative researchers are generally advised to use the largest sample size possible as the larger the sample size the more representative it is likely to be (Polit & Beck, 2006). This of course is only true if the study is conducted properly and the sampling strategy is not systematically biased. However, generally, researchers aim to have as large a representative sample size as possible. Sample size calculators are available to determine how many study participants are needed to get results that reflect the target population as precisely as required. They also enable the researcher to determine the level of precision in an existing sample. This is important as it enables the researcher to determine that the sample size is large enough that estimates will be sufficiently precise and any differences of importance are likely to be detected. The statistical software package, www.surveysystem.com was used to calculate sample size for this study. The initial sample size calculation indicated that given a total population of infants with cerebral palsy in the west of Ireland of 136, a sample size of 101 is required for a confidence level of 95% with a confidence interval of + or – 5.

One of the main disadvantages with the type of postal requests to participants for consent used in this study is that the response rate may be very low. Denscombe (1998) suggests that researchers are lucky to achieve a response rate of 20%. Buckingham and Saunders (2004) suggest that rates as low as 10% are not uncommon. Response rates of 10-40% for first mailings are described by O’Rourke (1999) while Kelly and Long (2000) suggest that many postal requests will not achieve a response rate of over 50% in most situations. Increasing the size of the sample increases the likely precision of the sample therefore reducing the likelihood of sampling error (Bryman, 2004). In addition to being important for the validity of the study, an adequate response rate is also necessary for the cost effectiveness of a study. The WICPR covers the birth period 1990-2000 and contains data on 136 children. As the sampling frame in this study was limited to 129 living potential participants, efforts were made to maximise the response rate by using the techniques described below recommended in the literature by Oppenheim (1992), Dillman (2000), Edwards et al (2002) and Curtis and Redmond (2009).

3.5.5 Enhancing the Response Rate

The response rate refers to the proportion of respondents in the sample who completed and returned the consent forms. Non-response is defined as the degree to which a researcher does not succeed in obtaining the co-operation of all potential respondents (Barriball & While, 1999).

Response rates matter for two reasons. Firstly, if the sample size is reduced the study loses statistical power and therefore may not be able to identify (and quantify) any true associations (Iversen et al, 2006:167). Secondly, a low response rate means that participation bias is almost inevitable (Iversen et al, 2006:167). Participation bias, also referred to as non-response or selection bias, is a widely recognised problem in epidemiological studies that require participant consent. The requirement to seek consent will introduce selection bias as not all the people invited
to participate in the study actually agree to do so and those most likely to respond are likely to be those for whom the study has greatest salience (Iverson et al., 2006; Polit & Beck, 2006). Systematic differences in the characteristics of those participating in research compared to those who do not have been reported and include clinical, social and ethnic biases (Parkes et al., 2006). Non-responders may be atypical. This invariably leads to questions about whether or not the responding sample was representative of the sample initially approached. In this study, it was not possible for the researcher to do any comparative analysis of responders versus non-responders, as the researcher did not have permission to access any information other than names and addresses of the sampling frame. Therefore, no firm conclusions can be drawn regarding whether responders differed significantly from non-responders. Bias will be discussed further in section 3.9 on the study limitations.

Various techniques were employed to enhance the response rate. Oppenheim (1992) suggests that the appearance of the first envelope is a significant factor for increasing the response rate. He argues that it has a better chance of being opened if it looks professional. Thus, for this study the envelopes containing the study information and request for consent were addressed using typed address stickers. Full stamps as opposed to franking were used as suggested by Oppenheim. Curtis and Redmond (2009) suggest that a well-designed invitation to participate is one of the easiest ways to increase the response rates. They advise that the letter should be brief, but informative, well written, motivating and signed by the researcher. Thus, for this study the detailed, comprehensive, invitation to participate was professionally presented on University headed paper and signed by the researcher (Appendix 3.5, 3.9). Curtis & Redmond (2009) also advise that it is important to reduce the respondent burden. This was achieved by ensuring that the consent process was easy to complete and demanded little effort on the part of the respondent. Stamped addressed return envelopes were included to further ease the reply process. Other factors that influence response rates are a clear commitment about maintaining confidentiality and privacy (Oppenheim, 1992; Dillman, 2000). Assurances about privacy, confidentiality, data protection and the right to withdraw were given in the information letter sent with the request to participate. The interest or involvement of the respondents in the topic is another factor cited in the literature as affecting response rates. Van Kenhove et al., (2002) found that high personal involvement in a topic acts as an intrinsic motivator for participants to engage with and respond to postal approaches. As cerebral palsy is such a significant factor in the lives of children with cerebral palsy and their families there is no doubt that the sampling frame in this study was deeply involved and very interested in the topic. This was reflected in the response rates.

Before the request to participate was posted a precise plan was made for monitoring the response rate and for the follow up procedure. Follow up with reminder letters is essential to improve response rates (Oppenheim, 1992; Curtis & Redmond, 2009). A spreadsheet was developed to record the return of each consent form. Non-respondents were thus identified through unreturned consent forms. This guided the timing of the follow-up letter. Once two weeks had lapsed after the specified return date a reminder letter was sent out to any non-respondents (Appendix 3.6). It was not feasible at this stage to anonymise respondents as the researcher needed to know which
participants had consented to their records being accessed and which participants had not. A stamped addressed return envelope was included with the reminder letter. This process was repeated again a second time 2 weeks later. A thank you post-card was sent 2 weeks after that. Details of the sample population yielded by this recruitment procedure will be described in chapter 4.

3.6 Data Collection

The relevant data for this study were collected and recorded systematically for each participant on a data extraction form and organised in a way to facilitate computer entry. Data collection is the precise, systematic gathering of information relevant to the study aims and objectives (Burns & Grove, 2001). As is usually the case for studies in the positivist paradigm, quantitative methods using formal instruments were employed for systematically collecting the relevant data. Peat (2002) recommends that structured quantitative approaches to collecting data are appropriate when researchers know in advance exactly what information they need to know and can, therefore, frame appropriate questions to obtain the needed information. Having reviewed the literature, the researcher was aware of the type of antenatal, intrapartum and neonatal information that was required to meet the aims and objectives of the study. Accordingly, for this study, the relevant questions relating to cerebral palsy and its associated factors were formatted as a data extraction form.

3.6.1 Design of data extraction form

A structured data extraction form consisting of a series of questions was deemed appropriate for this particular study. Peat (2002) advocates that data collection procedures should be standardised so that the conditions and mode of administration remain constant throughout. The use of the structured data extraction form ensured constancy throughout the study and across all the participants. A well-constructed questionnaire instrument allows the collection of reliable and reasonably valid data relatively simply, cheaply, confidentially and in a short space of time (Anderson, 1990; Parahoo, 1997; LoBiondo-Wood and Harber, 2002). The data extraction form utilised to obtain data relevant to the study aims and objectives was inexpensive and could be used without prior training. A detailed search of the literature identified a number of suitable instruments to elicit data about cohorts of children on cerebral palsy registers. A number of studies looking at similar data were identified in the literature review (Badawi et al 1998a & 1998b; Johnson, 2002; Greenwood et al, 2003; Parkes et al, 2005; Thorngren-Jerneck & Herbst, 2006; Strijbis et al, 2006; Studdert et al, 2006; Sigurdardottir et al, 2009). The data collection instruments used in those studies were examined. Those instruments had not previously been used in an Irish context nor had they been used exclusively with midwives. Although various aspects of each instrument were useful, no one instrument covered all the issues that needed to be addressed for this particular study. Therefore, for completeness of data, the researcher decided to design a new data extraction form that directly targeted the type of data of interest for this particular study (Appendix 3.7).
The resulting data extraction form emanated from a review of the associated literature, consultation with experts in the field and consideration of instruments from previous studies. It was important to ensure that the items on the data extraction form reflected the research aims and objectives and were relevant to the current research study. Hence, the information collected was essentially related to the prevalence and distribution of variables associated with cerebral palsy and intrapartum hypoxia. The data extraction form was compiled and discussed with the researchers’ supervisors and a statistician.

3.6.2 Content of data extraction form

The most important aspects considered when developing the data extraction form were the content, the presentation and the mode of administration (Steiner & Norman, 2003; Cluett & Bluff, 2006). Cluett & Bluff (2006) advocate that it is vital that care is taken in the design and administration of the questionnaire as this will affect the reliability and validity of the data collected. The items included on the data extraction form for this study reflect the key factors identified from the literature that are associated with cerebral palsy and intrapartum hypoxia. These items reflect the aims and objectives of the study. The final draft of the data extraction form consisted of 59 items that reflected the antenatal, intrapartum, neonatal and paediatric themes. The items were grouped into three topic areas; maternal data, neonatal data and paediatric data. The maternal data section included 29 items related to sociodemographic, antenatal and intrapartum factors associated with the mother. The neonatal data section included 22 items related to sociodemographic, antenatal, intrapartum and neonatal factors associated with the baby. The paediatric data section included eight items related to a subsequent cerebral palsy diagnosis.

Operational definitions were included in the data extraction form to ensure clarity around each data item required. Whitney (2000) advocates that when collecting data retrospectively from existing records, having a pre-defined guiding criteria or parameters for documentation will ensure accuracy and completeness of data collection. The use of the operational definitions in this study ensured that there was no ambiguity around the data required. Items on the questionnaire employed a mostly closed questions format. Boynton & Greenhalagh (2004) recommend closed-ended designs as enabling researchers to produce aggregated data quickly. The closed questions on the data extraction form were quick and easy to answer and involved the researcher selecting a response from specified options. The layout of the various items reflected the actual layout of the patient records to avoid the need for repeatedly flicking backwards and forwards through the source record. Peat (2002) advises that data collection forms must be designed to minimise any measurement error, to minimise missing data, to minimise bias and to make data easy to collect, process and analyse. The data extraction form designed for this study was a simple, easy to use, unambiguous, efficient instrument that generated all the information required to conduct this epidemiological cohort study.
3.6.3 Reliability and validity of the data extraction form

Before use in the study, the data extraction form had to be tested to ensure that it would collect the items intended and do so consistently and that it was a well-constructed and content-valid instrument. Quantitative researchers use several criteria to assess the quality and accuracy of a data collection instrument. Two of the most important criteria are reliability and validity (Polit & Beck, 2006). Expert researchers recommend that scientifically rigorous research studies must use data collection instruments for which validity and reliability are established and documented (Selby-Harrington et al, 1994). The reliability and validity of a data collection instrument have serious implications for the findings from the final data analysis. In quantitative research if the tools are considered valid and reliable, then it is assumed that the data that they collect should also be valid and reliable (Oppenheim, 1996; Watson et al, 2008).

Reliability is seen to reflect the accuracy, consistency and dependability of an instrument (Kelly & Long, 2000; Rattray & Jones, 2007). According to Collis and Hussey (2003), an instrument is reliable if when used by someone else to repeat a study the same results are obtained. Reliability testing focuses on three main aspects; stability, homogeneity and equivalence (Polit & Beck, 2006). Stability refers to the extent to which the instrument obtains the same results on repeated applications (Bryman, 2004). Homogeneity refers to the extent to which all the items assess the same characteristic or concept. Equivalence refers to the consistency of an instrument for different observers or raters (Polit & Beck, 2006). The literature is very clear about the need to establish empirically the reliability of instruments where questionnaires are used to collect data directly from subjects. The literature is less clear regarding situations where data are collected directly by a lone researcher through abstraction of information from medical records (Banks, 1998; Eder et al, 2005; Pan et al, 2005). For this study, deciding on the extent of reliability testing and the best methods to use proved challenging. Selby-Harrington et al (1994: 49) while reporting on instrument validity and reliability acknowledge that “the purpose of the study and the type of data collection instrument used will determine which methods or types of validity and reliability assessment are appropriate”

Having reviewed the literature and considered the function of the data extraction form in this study it was decided that empirical reliability testing was not necessary. Reliability testing is advocated when an instrument has been designed to measure a concept that has been conceptually defined (Bryman, 2004). The instrument in this study is not measuring a concept; it is merely collecting items of information from medical records. The items of information are not expected to be correlated with each other and so it is not appropriate to use the various indices of homogeneity. Many of the items recorded are actually dichotomous values. The data were collected retrospectively from pre-existing records and so the information is stable over time. The data items required were objective items and were defined clearly in the operational definitions. Empirical reliability testing is, therefore, not warranted for this particular instrument due to the diversity of items in the tool and the fact that the items are not testing a concept.
Reliability may be influenced by factors associated with the participant or the researcher and may also be affected by social or psychological factors (Cluett & Bluff, 2006). The main threats to reliability are said to be error and/or bias on the part of the subject, the observer and/or the instrument. When an instrument is reliable, bias due to the researcher’s influence is reduced. The structure and the wording of questions and response categories can reflect the researchers bias (Watson et al, 2008). This was a particular risk for this study as the question and response categories were created by the researcher. However, the data extraction form is based on the literature and clear criteria of measurement and interpretation were specified in the operational definitions that accompanied the items on the data extraction form. The use of a single researcher as opposed to a team of researchers further enhanced the reliability of the data extraction form by reducing the potential for inter-rater variance.

Having considered the issue of instrument reliability the researcher believes that the data extraction form used for extracting information from the records ensured that the appropriate data were selected and that they were extracted and recorded consistently.

**Validity** refers to the degree to which an instrument measures what it is supposed to be measuring (Gibbon, 1995). A research instrument is valid if it tests what it sets out to test and does so accurately. Seven types of validity have been identified: face, content, criterion, concurrent, predictive, construct, and convergent-discriminant (Gibbon, 1995; Bowling, 1997). However, Burns and Grove (2001) maintain that they are all inter-related and are varieties of the three main types: predictive validity, construct validity and content validity.

**Predictive validity** is a type of criterion validity. Criterion-related validity is concerned with how well the study performs in relation to other already validated measures of the same subject area (Cluett & Bluff, 2006). **Construct validity** is concerned with how well the construct under study is assessed. It is usually associated with abstract concepts, which may be difficult to define and measure and requires the application of statistical tests, usually factor analysis (Gibbon, 1995). As no other instrument exists that specifically records the same wide range of variables as the data extraction form for this study it was not possible for the researcher to measure either predictive or construct validity. Although this data extraction form shares the majority of core themes with many similar questionnaires it does not entirely cover the same content as any other single questionnaire. It has been suggested by Strickland (2006) that a priori validity exists when the developer of an instrument uses the literature to generate items for a questionnaire. All items on the data extraction form used in this study were generated from the literature so it could be argued that this confers validity.

**Content validity** is concerned with adequacy of coverage of the content area being measured (Polit & Beck, 2006). Each item on the data collection instrument should be there to address a characteristic that is under study and should be based on the literature (Gibbon, 1995). Face validity refers to an aspect of content validity that critiques the layout, phrasing and readability of an instrument. Face validity of the data extraction form in this study was evaluated by both expert review and discussion with the study supervisors. There is an element of subjectivity in most
Aspects of validity evaluation. An instrument’s content validity is based mainly on the judgement, logic and reasoning of the researcher with validation from peer review by practitioners having expertise in the domain of content (Wynd et al, 2003). However, in recent years researchers have begun to identify the need to find quantifiable methods for determining content validity. The empirical approach used to evaluate the content validity of the data extraction form used in this study was informed by Lynn’s (1986) paper ‘Determination and quantification of content validity’

Lynn (1986) advocates a 2-stage process for determining and quantifying content validity in new instruments. The first stage (development stage) identifies the domain of content through a comprehensive literature review. Cerebral palsy and its associated factors were identified as the domain of content in this study. The identification of the domain of content was followed by the generation of instrument items and the subsequent drafting of a data extraction form. Lynn’s (1986) suggested second stage (judgement stage) involves expert testing of the content validity of both the items and the entire instrument. This was done by sending a draft of the data extraction form to a panel of experts for peer evaluation during April 2010. There is no consensus on the number of experts required to validate an instrument. Recommendations vary from 3 to 20 (Slocumb & Cole, 1991; Grant & Davis, 1997). The draft instrument for this study was sent to 10 experts in the hope that at least 50% would respond. Individuals were chosen who had expertise in cerebral palsy (2 paediatricians & 2 obstetricians), in instrument development (1 PhD & 1 lecturer in research), in epidemiological research (2 database managers) and in clinical negligence litigation (2 solicitors). The responding experts are listed below in table 3.1. Ten people were chosen, as three is the minimum number recommended by Lynn (1986) for testing content validity and the researcher was aware of the possibility of a poor response rate or failure of agreement among the experts.

The draft data extraction form was electronically mailed to the expert reviewers. An explanatory cover email provided information on the study topic and aims along with information on the purpose of the data extraction form. A copy of the data extraction form and a set of guidelines for conducting the content validity evaluation were attached to the email. The expert reviewers were asked to use a Likert-type rating scale. Each expert was asked to rate each item on the data extraction form for relevance using the following scale:

1= not relevant
2= unable to assess relevance without revision
3= relevant but needs minor alterations
4= very relevant

This structured evaluation procedure, known, as the index of content validity, is the most widely used quantification of validity (Lynn, 1986). The experts were also asked to provide suggestions regarding any modifications, inclusions, revisions or exclusions of the items they felt were necessary. They were also asked to comment on the overall instrument. The content validity evaluation form (Appendix 3.8) and the letter of request were designed to place as little burden as possible on the experts in terms of time and effort. It was hoped that this would enhance the response rates.
Five of the 10 experts contacted returned the content validity evaluation. In keeping with Lynn’s (1986) recommendation, a content validity score of 3 or 4 was considered sufficient for item inclusion in the data extraction form. Fifty-nine of the 60 items were rated 3 or 4 by all expert reviewers. An item recording nucleated red blood cell count was queried by 4 of the 5 experts. This item was subsequently removed. The instrument content validity index was calculated by taking the total number of items having a score of 3 or 4 and dividing that by the total number of items giving an overall instrument CVI of 0.98 (Table 3.1). The literature recommends that a new instrument should have a minimum content validity index of 0.80 (Davis, 1992; Grant & Davis, 1997).

Table 3.1: Inter-rater agreement on a 60-item instrument by 5 expert reviewers used to assess content validity

<table>
<thead>
<tr>
<th>Area of Expertise</th>
<th>Number of items scoring 1 or 2</th>
<th>Number of items scoring 3 or 4</th>
<th>Total number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expert 1</td>
<td>Paediatrician</td>
<td>1</td>
<td>59</td>
</tr>
<tr>
<td>Expert 2</td>
<td>Obstetrician</td>
<td>1</td>
<td>59</td>
</tr>
<tr>
<td>Expert 3</td>
<td>PHD study on CP</td>
<td>1</td>
<td>59</td>
</tr>
<tr>
<td>Expert 4</td>
<td>CP database manager</td>
<td>1</td>
<td>59</td>
</tr>
<tr>
<td>Expert 5</td>
<td>Solicitor</td>
<td>0</td>
<td>60</td>
</tr>
<tr>
<td>Total number of items</td>
<td></td>
<td></td>
<td>300</td>
</tr>
</tbody>
</table>

Thus, the new data extraction form used in this study was objectively tested for content validity. Further alterations were made and the 3rd draft of the data extraction form was used in the pilot study.

3.6.4 Piloting of the data extraction form

Piloting the data extraction form is recommended to identify any ambiguities in the instructions, to clarify the wording of the items, to identify items that lack clarity and to ensure that it is appropriate and acceptable (Anderson, 1990; Bell 1999). Piloting is also recommended as contributing to ensuring the validity and reliability of the instrument (Parahoo, 1997). As the instrument was solely for the use of the researcher, piloting was conducted by the researcher. The draft data extraction form was piloted by using it to extract data from five sample medical records. As the study sample size was limited, these 5 cases were subsequently included in the final analysis. The researcher concluded that results from the pilot study indicated that the data extraction form was comprehensive and appropriate and presented no problems for recording data. Piloting showed the operational definitions to be well defined and clearly understood. Thus, the data extraction form was deemed suitable to provide data to meet the purpose of the study.

3.6.5 Administering the data extraction form

The data extraction form was subsequently administered by the researcher. The collection of data involved the researcher travelling to the various maternity units in the West of Ireland and accessing both maternal and neonatal hospital charts. Data extracted from the patient records
were anonymised using a numerical identifier to protect patient privacy and confidentiality. Data for the paediatric information section of the data extraction form was clarified by the information held on the West of Ireland Cerebral Palsy Register (WICPR). Data collection for this study commenced in September 2010.

3.7 Data Analysis

Analysis of data was undertaken to describe the presence of certain characteristics (exposures) and outcomes in the cohort and to examine the relationship between the exposures and the outcomes. The relevant exposures and outcomes were determined by exploring the literature relating to cerebral palsy. The exposures were; socio-demographic, antenatal, intrapartum and neonatal factors and the outcomes were cerebral palsy subtypes and associated impairments (learning, visual, hearing and seizure activity). In this retrospective cohort, study information about exposures was ascertained from past maternity and neonatal records. Information about outcomes was ascertained from the West of Ireland Cerebral Palsy Register. All 100 children in the cohort are still attending the cerebral palsy services and so have current records.

The data extraction forms, consisting of 59 items subdivided within 3 topic areas had been completed manually by the researcher from the medical records of each participant in the cohort. Data from the 100 completed data extraction forms were subsequently inputted into the computer, coded appropriately and analysed using the Statistical Package for the Social Sciences (SPSS) version 18.0 and the Cochrane Review Manager Software (RevMan) (The Nordic Cochrane Centre, 2008). SPSS is advocated by Cormack (1996) as a comprehensive and flexible statistical package to analyse and manage data as well as generate tabulated reports, charts and comprehensive analysis.

Accuracy of input was checked through a process of double data entry. There are a number of data verification methods available for identifying data input errors. Among those are valid range checks, filter checks, logical checks and double data entry (De Vaus, 2002). Double data entry is the process of a single person entering the same data on two separate occasions and thereby identifying errors in data entry (Gibson et al, 1994). The double data entry process was chosen for this study because there was one lone researcher and as the number of records was quite small (n=100) visual inspection for errors was very manageable. King and Lashley (2000) have described double data entry as the most commonly used quality assurance procedure to ensure that incorrect data is not entered into a record in a research study. However, it must be acknowledged that double data entry will not show up any errors made while extracting the data from the patient record. The same procedures were used for both the initial and the second entry of data. The data from the hardcopy version of the data extraction form were entered into the SPSS data file one study participant at a time. Data errors were found to be minimal and were appropriately corrected. Missing data were coded as missing values; ‘9999’ and ‘2222’ for not applicable.

Having collected the data and entered it into SPSS and RevMan, analysis of those data then took place. Collecting data is a crucial part of the research process but researchers must analyse and
make sense of data before presenting them to readers in ways that they can understand (Parahoo, 1997). Data analysis is therefore conducted to reduce, organise and give meaning to data (Burns & Grove, 2001; Saunders et al, 2003). Epidemiology is often classified as descriptive or analytic. Data analysis for descriptive epidemiology makes use of available data to examine how rates vary according to demographic variables, whereas, analytical epidemiology examines hypotheses of associations of suspected risk factor exposures with health outcomes (Szklo & Nieto, 2007:3). In observational designs, the researcher collects information on the characteristics, attributes or measurements of interest, but does not manipulate them in any way. Cohort studies are observational in design and are generally concerned with information regarding the prevalence, distribution and inter-relationships of variables in a population (Healy & Devane, 2011). Data analysis for this cohort study established frequency of occurrence of cerebral palsy, described the cohort and explored relationships between variables in the cohort where appropriate.

A typical measure of frequency of disease occurrence used in epidemiology is the prevalence rate. Prevalence refers to the proportion of a population who have a disease at a point in time and is calculated by taking the number of existing cases at a specified time and dividing by the population at risk at that given time (Webb et al, 2005; Nordness, 2006). Prevalence, therefore, is a measure of disease status rather than of newly occurring disease (Rothman et al, 2008). Live births and neonatal survivors are usually used as the denominator when calculating cerebral palsy prevalence. Prevalence rates for this study cohort were calculated per 1,000 live births and per 1,000 neonatal survivors with 95% confidence intervals. Prevalence rates were calculated using population data from the Central Statistics Office (CSO) and the National Perinatal Reporting System (NPRS).

Having calculated the prevalence rate, subsequent data analysis was undertaken to describe the cohort. Descriptive analysis enables the generation of meaningful information about the cohort from the large amount of numerical data collected. According to Fielding & Gilbert (2006), such analysis may include proportions, frequencies, means, standard deviations and range of scores for the study variables. A variable refers to a characteristic or attribute of an individual that can be measured or observed and that varies among the people being studied (Yang, 2010). Variables commonly measured in studies include gender, age, weight and socioeconomic status (Creswell, 2003). Descriptive data analysis for this cohort study was undertaken with regard to demographics and other baseline information to provide an accurate account of the characteristics of the cohort. The descriptive analysis was subdivided into a description of the maternal sample, the birth details of the children, the cerebral palsy subtypes, the cerebral palsy co-morbidities, the cerebral palsy aetiologies, the perinatal cases and the ACOG (2003) objective criteria. Data were analysed initially by obtaining frequency distributions of variables. Findings are reported in percentages, to the nearest whole percentage point and number of cases. Descriptive analysis presents summary statistics such as frequency distributions, central tendencies (means, medians) and results of variability measures (standard deviations, inter-quartile range). The summary statistics presented depended on whether the data were normally or non-normally distributed.
In addition to describing the cohort, data analysis was also conducted, where appropriate, to investigate relationships between variables and groups using inferential statistics. The basic structure of analysis in a cohort study is the comparison of different characteristics and the use of statistics to establish whether any relationship exists between the variables (Altman, 1991; Brink & Wood, 1998). The number of variables being examined and the level of measurement involved together with the degree to which the study is either purely descriptive or is attempting to explain associations between variables are the issues which will determine the nature of the statistical analysis (Kelly & Long, 2000: 34). In epidemiological studies, statistical analyses are typically organised around exposures, outcomes, confounders and effect modification (Hernan et al, 2002). In this study, statistical analyses were used, where appropriate, to examine the associations between the exposures (sociodemographic, antenatal, perinatal and neonatal factors) and the outcome (cerebral palsy subtypes and its associated impairments).

However, the mere existence of a relationship—even a strong one—between variables is not enough to warrant the conclusion that one variable has caused the other (Munro, 2001; Polit & Beck, 2006). In observational studies, the interpretation of observed associations needs great care (Altman, 1991). Findings from these types of designs do not establish causation; however, they provide information about associations between variables. They do not establish causation in part because these designs lack manipulative control of the independent variable. Only in randomised trials and other experiments can we reasonably ascribe an observed effect to be causal, because of the controlled nature of the investigation (Altman, 1991). Cohort designs are not interventional in the sense that treatment or interventions are not strictly controlled and randomisation is lacking (Whitney, 2000). Therefore, although cohort studies can provide information about associations between variables they cannot determine whether those associations are causal or not. Although statistical analysis from epidemiological studies have established associations between various sociodemographic, antenatal, intrapartum and neonatal factors and cerebral palsy no conclusions can be drawn about any of those factors actually causing cerebral palsy. However, inferences are made about causation in cohort studies by measuring the strengths of associations and the consistency of associations across a range of studies (Webb et al, 2005).

Inferential data analysis in cohort studies is often undertaken to determine risk rather than drawing inferences about causation (Bailey et al, 2005). Risk ratios are calculated where appropriate to determine whether there is an excess risk or perhaps a reduced risk of certain outcomes with certain exposures. Risk ratios are calculated, where appropriate, to determine whether there was a significant difference between the proportions of various characteristics in two comparison groups. Risk ratio is a measure of the absolute risk in one population as a proportion of the absolute risk in another (Nordness, 2006). If the frequency of the outcome is the same in all groups, then the ratio is 1.0, indicating no association between exposure and outcome. A ratio greater than 1.0 implies an increased risk and a ratio less than 1.0 implies a protective effect (Stewart, 2010). Results are reported as risk ratios with 95% confidence intervals. Confidence intervals suggest how confident we can be in the accuracy of our results. They allow researchers to account for random error in the
estimation process. A narrow confidence interval indicates good precision or little random error while conversely a wide confidence interval indicates poor precision (Stewart, 2010). Risk ratio results are considered significant if the value ‘1’ is not contained between the upper and lower confidence limits. Rothman et al (2008:151) advocate the use of confidence intervals in epidemiological studies as opposed to significance testing. They argue that significance testing is limited to providing a decision as to whether chance alone could have produced an association whereas confidence intervals provide estimation of the magnitude of associations as well as an assessment of the precision of the estimation method. Epidemiologists favour confidence intervals. Poole (2001:140) a renowned epidemiologist, has described the proliferation of p-values as ‘a pox spread upon the field of epidemiology’. Szklo & Nieto (2007:360) contend that when the 95% confidence interval of a relative risk does not overlap the null value, it is often used as a proxy for the presence of statistical significance (p<0.05). Of course, the accuracy of the inferential data analysis is dependent on the validity and reliability of the research process and the elimination and/or control of bias in the study. In non-randomised studies, inferential statistics do not provide valid probability statements about effects. Rather inferential statistics in such studies are often regarded as descriptive.

As is usual in quantitative studies, the analysis of data for this study took place after all the data had been collected (Black, 1999). Data analysis took place between May and June 2011. The researcher collaborated with a statistician and an epidemiologist during this phase of the research process, and was thus guided in the most appropriate ways to analyse and present the data. Having completed the analysis, results were compiled and inferences were drawn. These findings are presented later in chapter 4.

3.8 Ethical considerations

3.8.1 Introduction

Researchers have a responsibility to be aware of the ethical issues that pervade all aspects of research studies (Healy & Fallon, 2010). There were a number of ethical issues that were particularly relevant to this epidemiological study. Among them, issues of access to records, participant consent, participant capacity to consent, confidentiality and anonymisation of data. As the study involved accessing patient records, data protection concerns were significant. According to the Data Protection Commissioner (2007), the strong ethical obligations imposed on health professionals in relation to patients records are complemented by data protection requirements. Ethics refers to the appropriateness of the researcher’s behaviour in relation to the rights of those who become the subjects of the research or are affected by it (Saunders et al, 2003). As with all healthcare studies, the researcher in this case was obliged to apply certain ethical standards to the conduct of this study. The rights and values of people involved in research are protected by international codes and regulations such as, The Nuremberg Code 1949, The Declaration of Helsinki 1964, 1975, (Noble-Adams, 1999), the International Code of Ethics for Midwives (ICM, 1993), The Code of Professional Conduct for each Nurse and Midwife (An Bord Altranais, 2000).
and the Guidance to Nurses and Midwives regarding ethical conduct of nursing and midwifery research (An Bord Altranais, 2007). Emanuel et al, (2000) suggest seven requirements that provide a systematic and coherent framework for applying ethical considerations to research studies. These requirements are that the research study;

- Must have social or scientific value
- Must be conducted in a methodologically rigorous manner
- Must select participants fairly
- Must have a favourable risk-benefit ratio
- Must be independently reviewed
- Must have informed consent
- Must respect participants

The researcher used this framework to guide the ethical conduct of this epidemiological study throughout the research process.

3.8.2 Must have social or scientific value

In determining whether to proceed with a research study Emanuel et al, (2000) recommend asking the question; is the research worthwhile? For any study to be worthwhile, it must either have social or scientific value and should benefit participants and/or society as a whole. This epidemiological study has no specific direct benefits to individual participants in that it will not have any direct effect on their cerebral palsy. However, the study has the potential to confer social and scientific benefits in terms of knowledge and advancement of research information that may contribute to the cerebral palsy services or to addressing the issue of the prevalence of cerebral palsy and its associated impairments in the future. Epidemiological studies are acknowledged as having larger societal benefits than individual benefits. Epidemiological studies have contributed to tremendous advances in modern health care by enhancing our understanding of the natural history of diseases and the value of many interventions (Tu at al, 2004). In a similar manner, this study will enhance our understanding of the natural history of cerebral palsy and therefore, represents a worthwhile and valuable study.

3.8.3 Must be conducted in a methodologically rigorous manner

Emanuel et al, (2000) point out that research that is designed and conducted poorly may produce scientifically unreliable or invalid results and as such is unethical in that it may expose subjects to risks or inconvenience to no purpose. To ensure that this epidemiological research was designed and conducted properly a recognised observational study methodology was utilised. The cohort study was chosen as the most appropriate to provide the necessary epidemiological information. The research objectives warranted the collection of information essentially related to the prevalence and characteristics of certain factors associated with cerebral palsy as identified in the relevant international literature. The chosen study approach facilitated those objectives in a methodologically rigorous manner by using accepted principles and methods. Validity testing of the data extraction form used also ensured that it was methodologically rigorous.
3.8.4 Must select participants fairly

As with any research study, participants were selected for this epidemiological study in the belief that they were best placed to meet the study aims and objectives. As well as accessing maternal records, this study also involved examining records of children with cerebral palsy. As children, and cerebral palsy sufferers, these participants represent vulnerable groups (National Disability Authority, 2006). Vulnerable groups, including children and those with physical or intellectual difficulties, require special ethical consideration during the research process because of uncertainties about their capacity to provide informed consent to research participation (Iacono, 2006). Although it is important that vulnerable groups are not targeted for research that potentially places them at risk, it is also important that vulnerable groups are not consistently excluded from research due to their status as vulnerable groups. In selecting participants for this study, the researcher tried to achieve a fair balance between the danger of overprotecting potentially vulnerable groups and denying such groups the opportunity to participate in research. Cerebral palsy is one of the most severe disabilities in childhood and makes heavy demands on health, educational and social services as well as on families and children themselves (SCPE, 2000). It is therefore imperative that studies continue into this condition despite the fact that children with cerebral palsy and their families represent vulnerable groups. Jollye (2009) in a study exploring parents’ decisions to enrol their children in research trials found that parents expressed altruistic principles around the decision. Jollye’s studies found that once the parents were satisfied that the benefits outweigh the risks they made their decision to participate because they wanted to contribute to future care.

In selecting potential participants, the concepts of self-determination, consent, freedom from coercion and right of withdrawal along with the ethical principles of justice and fair treatment ensured the fairness of the selection process. The participants in this study were not offered any form of compensation or inducement.

3.8.5 Must have a favourable risk-benefit ratio

Cluett and Bluff (2006) recognise that while research often has the potential to lead to advances in knowledge and practice it also has potential risks. As with all research studies, the researcher had an ethical duty to balance potential benefits against potential risks and to minimise potential harm to the greatest extent possible, thus safeguarding and protecting participants (Emanuel et al, 2000). All aspects of the study from the design, to the data collection, to the data analysis, to the dissemination of results were considered from a risk benefit analysis perspective by the researcher, with the needs of the participants taking precedence at all times over the desire of the researcher to conduct the study. With a letter, as opposed to any direct contact with the participants, this research was minimally invasive and therefore did not present any direct threat to the wellbeing of the participants. Where any potential risks were identified, steps were taken to minimise them. For example, the risk of breaching privacy was minimised by requesting consent from participants to access their records. The potential risk of harming vulnerable participants was minimised by
following the guidance of the (LRC) Law Reform Commission (2005) Consultation Paper on Vulnerable Adults, Capacity and the Law. The potential risk of breaching confidentiality was minimised by removing identifiers from the data extracted from the patient records.

In keeping with the interrelated ethical principles of beneficence and non-maleficence, this research should benefit participants and/or society as a whole while not placing any undue burden on, or doing any harm to the participants. The risks associated with epidemiological research should not be equated with interventional research. Existing research about study participants attitudes tend to support the view that the risks of epidemiological surveys, even when direct contact is made, are low (Iversen et al, 2006). Epidemiological research is usually a positive or at worst neutral experience for participants. This epidemiological research has no specific direct benefits to individual participants but equally it does not place participants under any undue burden. In this study, the risk to participants is minimal, the benefit to them directly is also minimal but the potential benefits to society and future patients are great. This ensures that the study has the justifiable risk benefit ratio advocated by Emanuel et al, (2000).

3.8.6 Must be independently reviewed

Emanuel et al, (2000) contend that the many diverse interests of researchers can generate conflicts that may unwittingly distort the judgement of even well intentioned investigators regarding the design, conduct and analysis of research. It is for this reason that independent review is so important. As this study was conducted as part fulfilment for an academic reward its entire process was consistently reviewed by academic supervisors. In addition, prior to initiating the study, the researcher obtained appropriate approval and permission to conduct the study from the relevant local HSE ethics committees (Appendix 3.1), and the Faculty of Health Sciences Ethics Committee, National University of Ireland, Galway (Appendix 3.2). In all, a total of 7 ethics committees reviewed the study. The research ethics committee provided an independent review of the studies compliance with ethical requirements. The ethics committee reviews provided guidance for the researcher in protecting the rights, dignity, wellbeing and safety of participants thus ensuring they are protected from unethical practices. Independent review also introduced accountability to the study and ensured that the risk benefit ratio was favourable so that no exploitation of participants took place.

3.8.7 Must have informed consent

The need for consent to access medical records for epidemiological study is the subject of intense debate in the literature. Obtaining explicit patient consent to access data in the context of epidemiological studies is often argued to be impractical, too costly and unnecessary as there are only very small risks to the patients involved and there are large benefits to society from the research conducted (Verity & Nicoll, 2002; Tu at al, 2004; Al-Shahi et al, 2005; Wendler, 2006). It is commonly argued that a blanket requirement for consent from every participant in observational research may bias study findings. The representativeness of a sample might be seriously compromised if the likelihood of obtaining consent were markedly influenced by factors such as the
severity of the child’s problems, the family’s level of satisfaction with existing services or literacy issues (Goodman & Yude, 1996). Al-Shahi & Warlow (2000) argue that although explicit written consent is essential for most trials of any intervention, it is an unrealistic requirement of epidemiological research and audit, particularly if these rely on huge quantities of previously collected data. Although it is true that this particular study was primarily concerned with the collection and analysis of pre-existing data the researcher did ask permission from the patients to access that data. This was done in the spirit of respect for autonomy and in keeping with the data protection legislation of this country. Aside from the need for consent in data protection, the role of consent in ethical terms is to safeguard patient autonomy.

3.8.7.1 Autonomy

Autonomy includes the right to self-determination. Self-determination means that the prospective participants have the right to decide voluntarily whether to participate in a study without coercion, covert data collection or deception, and without the risk of incurring any penalties or prejudicial treatment (Noble-Adams, 1999). The right to self-determination and the right to full disclosure are major components on which informed consent are based (Polit & Beck, 2006; Buckley et al, 2011). In giving consent initially for their child’s information to be entered on the WICPR parents had also given consent for that information to be used in future studies. However, it is generally held that explicit consent should be obtained to use personal data for research, especially secondary research when people who are not part of the original clinical team need access to the data (Kalra et al, 2006). The researcher in this study is not a member of local healthcare staff and felt that to uphold the right to self-determination participants should be asked for explicit consent for this particular study as opposed to relying on the blanket consent given to the WICPR. The Data Protection Commissioner (2007) proposes that the most straightforward way in which access to patient identifiable information for research purposes can take place, is with the consent of the person for the intended use. Hence, an explicit consent form and an accompanying information letter were used during the formal consent process of this study.

3.8.7.2 Consent and capacity

This study involved the collection of data from the records of mothers and their children. Consent was requested granting permission to the researcher to access such records. As the study cohort included people of varying ages, the consent process was complex. Anyone over 18 years old is legally an adult. The mothers in this study, as competent adults, consented for themselves, allowing the researcher access to their records. Currently, in Ireland, in law anyone less than 18 years old is actually a minor/child. Under section 2 of the Age of Majority Act 1985, persons under 18 who have not married are minors in law and generally do not have legal capacity (Law reform Commission (LRC), 2005). In discussing vulnerable groups, international ethical guidelines recommend that in all cases permission to invite vulnerable children under 18 to participate in research must be sought from parents or guardians (CIOMS: Council for International Organisations of Medical Sciences, 2002; Children’s Research Centre, TCD, 2006; National Federation of Voluntary Bodies, 2006; Sheikh, 2008). Although the shift in recent years from a
medical to a social model of disability encourages independent consent for daily living, personal and medical matters, the international recommendations recognise that participation by vulnerable groups in research warrants special protection. Following this guidance, the mothers in this study consented for their children less than 18 years of age. At the same time, it is acknowledges that in keeping with the UN Convention on the Rights of the Child (1989) children should be involved in decisions that affect them. This practice is described in the literature as assent, affirmative agreement or supported decision-making. The children under 18 years old in this study were afforded the opportunity to be involved in the assent process based on their individual ability.

The issue of consent for the children with cerebral palsy who are now over 18 years of age presented an ethical dilemma. Respect for autonomy considers the individual as an independent person who is able to make choices for him/herself (An Bord Altranais, 2007). The Law Reform Commission (2005) recommends that the law on capacity should reflect an emphasis on capacity rather than lack of capacity and should be enabling rather than restrictive in nature thus ensuring that it complies with relevant constitutional and human rights standards. In the absence of a legal determination, the presumption should be of capacity rather than incapacity. Therefore, it should be assumed that a person can make his or her own decision unless proven otherwise by formal independent psychological testing of capacity (LRC, 2005). To demonstrate capacity individuals should be able to; understand in simple language what the proposed action is, its purpose and nature and why it is being proposed; understand its principal benefits, risks, and alternatives, understand in broad terms what will be the consequences of not receiving the proposed treatment and retain the information for long enough to make an effective decision (MHB, 2004). Having considered all this guidance in the literature, the researcher decided in the spirit of inclusion and the protection of participant’s rights, that, for this study, the capacity of children with cerebral palsy who are now over the age of 18 was assumed and thus they were given the option of signing their own consent.

At the same time, the potential for lack of capacity had to be considered. Some individuals may have diminished levels of autonomy and the matter of determining levels of capacity may be very complex. In the context of this study, it had to be acknowledged that people with cerebral palsy might not be physically capable or intellectually competent to give informed consent. The researcher was acutely aware of the need for sensitivity around the issue of highlighting the levels of capability or lack of capability in people with cerebral palsy. The difficulty in making decisions about capacity in this study was compounded by the fact that prior to sending out the request for permission to access records the researcher had no way of knowing the extent of intellectual or physical disability for any of the potential participants. Iacono (2006) recommends that decisions about capacity must be made on an individual basis for both the potential participant and the specific research. The Data Protection (Amendment) Act, Section 2A (2003) holds that where the data subject by reasons of his or her physical or mental incapacity or age, is or is likely to be unable to appreciate the nature and effect of such consent, it may be given by a parent or guardian as proxy consent.
3.8.7.3 Proxy Consent

The practice of proxy consent for vulnerable children is based on the belief that the proxy, usually a parent, is motivated towards and capable of representing and safeguarding the child’s interests and rights (Inclusion Ireland, 2005; Long & Johnson, 2007). Long and Johnson (2007) acknowledge that when children are unable to determine what is in their best interests, parents are normally the best alternative decision makers. It must be acknowledged that the subject of proxy decision making for vulnerable groups has been the cause of considerable concern among stakeholders in Ireland for a number of years. The system of proxy decision making, although widely used and accepted, is informal and has no basis in law. In an attempt to regularise this ambiguous situation, the Department of Justice has drawn up a discussion document called the Mental Capacity Scheme (2008). This is currently undergoing consultation before the preparation of a Bill for legislation. It is hoped that the Bill, if enacted would bring in a definition of capacity, abolish the ward of court system and allow for personal guardians (O’ Carroll, 2009). In any event, in the absence of specific legislation at this time, the researcher in this study adopted a philosophy of supported decision making where a parent could determine, in conjunction with their child, who should sign the consent. Thus, proxy consent was utilised for young people over 18 years of age who were unable to sign their own consent form. This approach was adopted by the researcher in the belief that a proxy, usually a parent, is the advocate for these children from birth and therefore there is no reason to doubt that advocacy into adulthood.

The only potential alternatives to the approach adopted by the researcher in this study for the (few) over 18 year olds would be to either exclude them from the study or submit them to formal independent psychological testing of capacity. The researcher is of the opinion that neither of these options would have achieved a favourable risk benefit ratio without undue burden on the participant. As this study represented no direct threat of harm to participants, the approach taken by the researcher was to leave it up to the proxy, usually the parent, to decide in conjunction with their child whether the young adult was able to consent for himself or herself. Anecdotal evidence suggests that, in reality, this is how decisions are currently made in Ireland in families with persons with a disability. In a speech about surrogate decision making for vulnerable adults, the Chief Executive Officer of Inclusion Ireland, Deirdre O’Carroll (2009), suggested that in general, day-to-day living decisions tend to be made on an informal basis and are usually appropriate, necessary and made in the persons best interests. Thus, there is no reason to doubt such a decision making process in the context of this study. The LRC (2005) recommends that a common sense approach should be applied in determining when a separate functional assessment of capacity is merited. The researcher did not believe that a separate functional assessment of capacity was merited in this situation.

In summary, having reviewed all the literature and considered all the options, the researcher concluded that the best approach for this particular study and this particular cohort was for:

- Mothers to consent for themselves.
- Mothers to consent for their children less than 18 years old as they represent a vulnerable group participating in research.
- Children under 18 years old to be included in the decision making process.
- Over 18 year olds to consent for themselves.
- Proxy consent to be given by mothers for any over 18 year olds who are unable to consent for themselves.
- Decisions regarding ability to consent to be made within the family as per all other decisions in these people’s lives.

The request for consent included a detailed, comprehensive information letter to ensure full disclosure. Assurances about privacy, confidentiality, data protection and the right to withdraw were given in the information letter and provided for in the design and conduct of the study. Three different consent forms were used (Appendix 3.9 & 3.10). One for mothers, one for children with cerebral palsy who were under 18 years of age and another for children who are now over 18 years of age.

### 3.8.8 Must respect participants

Participants in this research study were not viewed as a means to an end but rather as partners in the research process. Ethical requirements for research do not end with the signing of a consent form but encompass the actual implementation, analysis and dissemination of research (Emanuel et al, 2000). Participants in this study agreed to allow the researcher to access data in their records to meet the aims and objectives of the study but at all times they remained the owners of that data and were respected as such. Respect for human dignity and autonomy encompasses not just the right to self-determination about our bodies and how they are treated, but also to information about our lifestyle, our health and ourselves. The right to control who knows the things about us that we regard as private is integral to our sense of self and sense of identity (O’Brien & Chantler, 2003). Respect for participants was demonstrated in this study by respecting their right to privacy and confidentiality and by full disclosure.

#### 3.8.8.1 Privacy

The right to privacy denotes the freedom for the participants to determine the time, extent and general conditions under which his/her private information will be shared or withheld from others (Noble-Adams, 1999). This right to privacy was upheld by asking for explicit, informed consent before accessing participant’s records. Informed consent is a voluntary, explicit agreement given by the participant without coercion (Holloway & Wheeler, 1995). Full disclosure was a prerequisite for informed consent. Full disclosure means that the researcher has fully described the nature of the study, the person’s right to refuse participation, the researcher’s responsibilities and the likely risks and benefits (Polit & Beck, 2006). This was done using an information letter accompanying the consent form.

Jacobsen (2009) describes the goal of the consent information letter as to educate potential study participants about the purposes of the study, the risks and benefits of participation, the study procedure and to allow individuals to make their own informed, autonomous and voluntary decision.
about whether to participate in a research project. The researcher used these goals suggested by Jacobsen as a framework in designing the comprehensive information letter that was provided to all participants with the request for consent. An Bord Altranais (ABA, 2007) recommendations further enhanced the design of the information letter. An Bord Altranais (2007) recommends that to ensure informed consent the researcher must state who she is, the purpose of the research, how it will be conducted and what will be done with the results obtained. The information provided should be sufficient, and communicated accurately in an understandable way using appropriate language or mechanisms. A copy of the comprehensive, explanatory information letter accompanying the consent form is available in Appendix 3.5. Assurances about privacy, confidentiality, data protection and the right to withdraw were given in the information letter and provided for in the design and conduct of the study.

3.8.8.2 Confidentiality

Throughout the study, the researcher was responsible for ensuring the confidentiality and privacy of the research participants and the data obtained from them. Confidentiality and privacy was maintained through the previously described consent process and also by removing the patient’s identity from the study data once it was extracted from the medical records. When research can be conducted on anonymous data, this is the most desirable option (Sheikh, 2008). However, receipt of data in an anonymised format will not always be possible. For this particular study, although the data extracted from the patient’s records were de-identified using a numerical identifier it was not possible to obtain the actual patient records in an anonymous format. There are only two ways in which the researcher in this study could have received the patient records in an anonymous form. Firstly, if someone, somehow, removed every single nominal identifier from the entire chart. This was obviously impractical, as it would involve defacing multiple official medical records. Secondly, if a licensed data controller extracted the data from the records and gave it to the researcher in anonymous format. Although this would have been very convenient, it was not within the remit of the researcher in this particular study to delegate that work. Therefore, charts were obtained by the researcher as identified records and the data extracted was then immediately de-identified by the use of a study identity number on the data extraction form.

The researcher acknowledges that the initial receipt of patient identifiable information presented data protection challenges but believes that the steps taken to manage the challenges represents what the data protection commissioner (2007) describes as a common sense approach to such challenges. Strobl et al, (2000) advise that if full anonymisation is not possible or the design of the study does not permit it, the use of pseudonymous data should be considered. The concepts of anonymisation and pseudonymisation are recognised in the literature and in data protection legislation. Anonymisation refers to rendering data irrevocable anonymous in that it cannot be linked to the individual. Pseudonymisation involves separating personally identifying data from substantive data but maintaining a link between them through an arbitrary code (Lowrance, 2002). Sheikh (2008) in his legal commentary on the effect of the data protection acts on public health research recommends that if the researcher receives identifiable data, where possible attempts should be made by the researcher to render the data as anonymous (make unidentifiable) or
pseudonymise (make indirectly identifiable) at the earliest stage possible. Pseudonymisation was the approach adopted by the researcher for this study. The medical records were obtained in identifiable format but the data extracted was immediately de-identified. The data extraction form used in this study was designed to ensure confidentiality and privacy by the use of a numerical identifier and choosing to omit any information that would identify the participants. Participants consented to this approach.

All data collected were accessible only to the researcher and the researcher’s supervisors. Participants were made aware of this. Participants will not in the future be identified in any reports or publications. Data were and will continue to be stored in a secure place in keeping with the Data Protection (Amendment) Act, 2003.

3.9 Potential Limitations

There are a number of methodological limitations to this study that must be acknowledged. Limitations are restrictions in a study that may limit the credibility of the findings and restrict the population to which the findings can be generalised (Burns & Grove, 2001). Scientific research implies the exercise of objectivity from the inception of the research idea, the design of the study, the methods used, the process of carrying it out and the analysis and interpretation of the research results (Bowling, 2002). Research errors such as faulty research procedures, poor sampling and inaccurate or misleading measurement, can undermine the validity of a study (Collis & Hussey, 2003). The strength of the research design adopted for this study was instrumental in protecting the validity and reliability of the overall study and its findings. Specific limitations of this study relate to external validity and the potential for errors.

Generalisability is a criterion used in quantitative study to assess the extent to which study findings can be applied to other groups and settings (Polit & Beck, 2006). It is sometimes referred to as external validity. External validity concerns how far the results obtained in the study population holds true for other people in other situations (Mulhall, 1996). External validity is not of primary importance for this study. This study chose only to represent a named cohort of the population of children with cerebral palsy and does not claim generalisation of the final data to the wider population. It is possible that the findings could be related to similar populations and settings but further in-depth research would be required before such a generalisation could be concluded. The use of non-probability sampling affects the extent to which the results can be generalised beyond the sample used in the study.

Internal validity refers to the extent to which the results obtained are a true reflection of the study population itself (Mulhall, 1996). Both internal and external validity are important but it is internal validity that is of primary importance. Studies that have a high internal validity always have some value, even if the external validity is low (Moon et al, 2000). There are many sources of bias that threaten the validity and reliability of research studies and it usually occurs due to faults in the way the study is planned and carried out.
Bias is the result of any process that causes observations to differ from true values in a systematic way and can arise from a number of sources including the researcher, the participants or the measurements used. The strength of the relationships that are measured in any type of study can be significantly influenced by factors that are a direct result of the study design and methods used (Peat, 2002). Thus, bias can lead to an erroneous inference about the importance of the relationships found (Brink & Wood, 1998). This was particularly relevant in this study, which explored relationships between various antenatal, intrapartum and neonatal factors and cerebral palsy. Three general factors are recognised as reducing the internal validity of a study: bias (systematic error), chance (random error) and confounding (Moon et al, 2000).

Selection bias refers to a distortion resulting from the manner in which participants are selected into the study population. Selection bias can lead to an underestimation or overestimation of both descriptive statistics and analytical statistics. The way in which subjects are identified, approached and respond to invitation to participate in research can be a major source of bias in epidemiological studies (Parkes et al, 2006). It is broadly accepted that the need for participant consent has the potential to introduce selection bias into epidemiological studies (Al-Shahi & Warlow, 2000). Due to the selection bias introduced by the consent process the full potential of this cohort study may not have been realised. Potential participants were excluded if they did not respond to the request for written consent to participate. Moon et al, (2000) acknowledge that the response rate to the selection process may introduce bias in that non-responders may be atypical or differ from the responders in some systematic way. Selection bias occurs when the subjects studied are not representative of the target population about which conclusions are to be drawn (Coggon et al, 2003). The researcher was not able to establish if there were any significant differences between responders and non-responders. Therefore, the extent to which the findings can be generalised to the overall population of children with cerebral palsy in the West of Ireland is uncertain. This limits the usefulness of the data for service planning. However, selection bias was minimised in this study by rigorous recruitment procedures and attempts to maximise participant response rates.

Measurement bias occurs when the independent variable or dependent variable is collected, measured or classified in a way that is systematically inaccurate (Stewart, 2002; Coggon et al, 2003). Defective measuring instruments are a major source of measurement bias. Measurement bias was minimised in this study through the very careful design and testing of the standardised data extraction form. The data extraction form used closed-ended questions with the order and wording predetermined so that they could be administered for each participant in exactly the same manner, thus minimising potential bias. The use of very clear and rigorous operational definitions also helped minimise potential measurement bias. The researcher is confident that the data extraction form used for extracting information from the records ensured that the appropriate data were selected and that they were extracted and recorded consistently.

Chance (random error) occurs due to chance alone. Chance is more likely to be a factor if the sample size is small and the study lacks the power to detect the true estimation of an association
The potential for random error was minimised by robust study design and correct statistical tests during data analysis. The use of confidence intervals allowed the researcher to account for random error in the estimation process. Confidence intervals provide estimation of the magnitude of associations as well as an assessment of the precision of the estimation method.

Confounding occurs when two factors are associated, and the effect of one is confused with the effect of the other (Mulhall, 1996). Confounding occurs when an external factor (or factors) distorts the relationship between the primary exposure and outcome of interest. To be a confounder, the factor has to be related to the exposure and it also has to be an independent risk factor for the disease being studied (Stewart, 2002). It is important to note that there can be relationships between variables that do not constitute confounding. Confounding is not introduced by a factor that is simply an intermediate step in the causal path between exposure and disease (Moon et al., 2000). The most important confounders are those that are both relatively common and strongly related to exposures and disease outcomes (Webb et al., 2005).

Confounding itself is not necessarily an error. However, failure to take the confounding variable into account when analysing data and interpreting the results of the study is an error. Confounding may result in the strength of an association being either over or under-estimated. Therefore, it is important to take steps to manage confounding because failure to take the confounding variable into account may cause a researcher to conclude that a factor increases the risk of an outcome when in fact it does not (Type I error), or the researcher may fail to detect an association that does in fact exist (Type II error). In practice, it is rarely possible to remove all confounding so some residual confounding will remain (Webb et al., 2005). Nevertheless, there are several methods available to manage confounding.

Randomisation is the best method but can only be used in intervention studies. Matching according to select participant characteristics is another method to control for confounding but may not be feasible for all study designs. As this was a cohort study, restriction was used to deal with confounding at the design stage through careful sample selection using inclusion and exclusion criteria. Confounders were also managed during the analysis of the study through stratification (Szklo & Nieto, 2007). Stratification involved dividing the sample into subgroups, where appropriate, on the basis of characteristics that could potentially have confounded the analysis. Subgroups were stratified by gestational age, mode of birth, Apgar scores, cerebral palsy subtypes, additional impairments and aetiology where appropriate. While multivariate modelling may also be used to control for confounding (Szklo & Nieto, 2007), such models were not feasible for this study due to small numbers in the sample.

The potential for observer bias must also be acknowledged in this study. It is true that the measurement process may be flawed by individuality and perception. Observer bias may occur when the investigator is aware of the status of the exposure being investigated (Peat, 2002). The researcher was aware at the outset of this study that all cohort participants were affected by cerebral palsy. However, the data analysis examined associations between the various exposures
and the subtypes of cerebral palsy as opposed to the occurrence of cerebral palsy. Data on the various maternal and neonatal exposures were collected from the medical records separately from data on severity of cerebral palsy, which was subsequently collected from the cerebral palsy register. Thus, it could be argued that the researcher was in fact blinded to the outcome data when collecting the exposure data. It is however, the case that the researcher then linked both sets of data (exposure and outcome) before data analysis was performed. The potential for observer bias was minimised by the use of an objective outcome measurement tool for both exposure and outcome. Peat (2002) acknowledges that objective measurements are collected by instruments that are less easily open to interpretation or to influence by the observer. The use of rigorous operational definitions with the data collection tool removed any ambiguity around interpretation of measurements. The use of the data extraction tool standardised the data collection procedure so that the conditions and mode of administration remained constant throughout. This further reduced the potential for bias and error.

As with any epidemiological study, the researcher in this study made efforts to minimise systematic error to increase the validity of the study. Efforts were also made to maximise the power of the study and thereby reduce random errors. It is very difficult to avoid bias and confounding completely but measures can be taken to reduce, eliminate and manage these factors. Webb et al, (2005) contend that some degree of error is inevitable but that this need not invalidate the results of a study. Yang (2010: 120) argues that error does not mean mistakes but refers to the discrepancy between what the study is supposed to achieve and what it has actually achieved. Known bias may be prevented by rigorous study design, which eliminates selection or measurement bias, and proper data analysis, which can correct for errors caused by confounding (Mulhall, 1996). The potential for bias and confounding in this study was taken into account in study design, the data analysis and the interpretation of results. Despite the limitations mentioned, the researcher believes that the potential benefits from conducting the study are far greater than its limitations. The researcher accepts these limitations as an unavoidable part of the research process. While recognising and accepting the limitations, methodological approaches were adopted in this study in an attempt to minimise them.

No outside funding has been received by the researcher for the conduct of this study. The researcher received a student stipend from the School of Nursing and Midwifery, National University of Ireland, Galway for the duration of this study, which was conducted as fulfilment of a doctoral programme. There are no conflicts of interest to disclose. Research findings have been presented truthfully and any limitations acknowledged. All of the above considerations contributed to the methodologically rigorous design and conduct of the study.
3.10 Management issues

3.10.1 Resources

The researcher of this study was the sole researcher conducting the study, analysing the data and writing the research report. The researcher had access to necessary information technology and SPSS as part of her work infrastructure.

3.10.2 Time scale

The research, from study design to completion, was conducted over 3 years. A time scale was drawn up to allocate specific time to each stage of the process. This promoted effective organisation and management of time. The study commenced with obtaining ethical approval by attending the ethics committee as requested. An extensive literature search was conducted during this time. Once ethical approval was granted, the data extraction form was designed, tested for validity and then piloted. The collection of data commenced in September 2010. Data was subsequently analysed during May to June 2011. The findings were collated and the thesis written up for submission in the autumn and winter months of 2011.

3.10.3 Dissemination of the findings

The dissemination of research findings is a critical aspect of the research process (Tarling, 2002). Dissemination is necessary in order to generate further discussion and interest in the subject among stakeholders. A comprehensive, written report, which clearly represents the research process from the identification of the research question, through the methodology to the study outcome and recommendations, will be made available to relevant and interested parties. A copy of the study will be made available in the thesis library in NUIG. Meetings, conferences, journal publications with a peer review process, national meetings and various research databases will facilitate dissemination of findings to a wider audience. Integrated into the body of this thesis are writings related to the research already published by me during the period of my registration on the PhD register.

3.11 Conclusion

This chapter has described the research process used to conduct this cohort study exploring cerebral palsy in the West of Ireland. The data extraction form used, validity and reliability testing, ethical considerations and limitations of the study have been discussed. Analysis of the data that were collected for this observational study is now presented in chapter 4.
Chapter 4

Results

4.1 Introduction

The methodological issues and procedures for the conduct of this cohort study have been outlined in chapter 3. This chapter presents a detailed description of the findings of the analysis of the study data. Data analysis was directed towards addressing the research objectives, which are as follows:

- To report the distribution of antenatal, intrapartum and neonatal factors associated with cerebral palsy in the cohort.
- To identify the availability of data in the maternal and neonatal records to facilitate application of the essential criteria for defining a causal relation between acute intrapartum events and cerebral palsy put forward by the Neonatal Encephalopathy and Cerebral Palsy Task Force Report (ACOG, 2003).
- To apply the ACOG (2003) criteria for defining acute intrapartum hypoxia in the cerebral palsy cohort.

In all 100 complete sets of data were analysed. Each data set comprised 59 items that reflected antenatal, intrapartum, neonatal and paediatric themes relevant to cerebral palsy. Data analysis was conducted using SPSS (Statistical Package for the Social Sciences) version 18 and the Cochrane Review Manager Software (RevMan) (The Nordic Cochrane Centre, 2008). Data are presented in tabular and graphical format where appropriate to assist in the presentation of results.

As the study is observational, as opposed to experimental, data analysis will confine itself largely to descriptive analysis.

The recruitment process and response rates are outlined. General prevalence rates of cerebral palsy in the geographical area covered by the study are summarised. The chapter then describes the demographic details and the clinical characteristics of the cohort. Both the maternal sample and the sample of children will be described.

4.2 Recruitment and response rate

4.2.1 Recruitment

Recruitment of the cohort for this observational study was through the West of Ireland Cerebral Palsy Register (WICPR). The area covered by the WICPR is predominantly rural, comprising counties Galway, Mayo, Sligo, Roscommon, Leitrim and Donegal. During the timeframe considered by the study (1990-2000), the area had a total population of 600,000 inhabitants (CSO 2002, census data) and 81,598 births. There were 465 stillbirths and 295 neonatal deaths leaving 80,837 neonatal survivors. The sampling frame consists of 136 children with cerebral palsy registered on the WICPR for the birth period 1990-2000.
4.2.2 Response rate

Of the 136 children with a confirmed diagnosis of cerebral palsy registered on the WICPR, 7 had subsequently died. These children were excluded from the study because it was felt that in the absence of any relationship with the researcher, parents may have been offended and upset by an approach from an unknown person. Consent to access data was sought from the remaining 129 children included on the WICPR.

Consent for inclusion in the study was received from 61 participants (47%) following the initial request. The first reminder yielded a further 20 participants, bringing the response rate to 81 participants (63%). A second reminder yielded a further 11 participants bringing the response rate to 92 (71%). A follow-up thank you postcard issued to all initial 129 people approached yielded another 10 participants which brought the final overall response rate to 79% (n=102). The overall response rate was calculated using the number returned divided by the overall sample size giving a total response rate of 79% which, according to Gillham (2000), is a good response.

Two of the participants were excluded because insufficient maternal or neonatal data were recorded in the available medical records. The two cases were born to mothers resident outside the region at the time of birth and so primary source records were not available. The recruitment process therefore yielded a usable study sample size of 77% (n=100). This is summarised briefly in Figure 4.1. This sample size is representative of the total population of 136 with a confidence level of 95% and a confidence interval of 5.06. This approximates closely with the initial sample size calculations as outlined previously in section 3.5.4.

![Figure 4.1 Summary of cohort recruitment process](image-url)
4.3 Prevalence of Cerebral Palsy during the Study Period

Information from the service providers suggests that there are 156 children with cerebral palsy in the West of Ireland born between 1990 and 2000 (Mongan, 2006). One hundred and thirty six of these children are documented on the WICPR. This represents the 87% of cerebral palsy children whose parents consented for them to be included in the population-based register. According to data from the Central Statistics Office (CSO) and the Economic and Social Research Institute (ESRI), there were 81,598 live births in the West of Ireland during that time. Therefore, the birth prevalence of cerebral palsy for the years 1990-2000 was 1.9 per 1,000 live births (95% confidence intervals [CI] 1.6-2.2). Data from these sources indicate that there were 80,837 neonatal survivors during that time and so the prevalence of cerebral palsy is 1.92 per 1,000 neonatal survivors (95% CI 1.6-2.2).

4.4 Description of the Sample

In reporting this research study, a descriptive analysis of data is provided to demonstrate patterns and regularities that are common to the cohort sample. The characteristics of this study sample that will be described include a description of the maternal sample, the birth details of the children, the clinical subtypes of cerebral palsy, the co-morbidities present in the form of additional impairments and the likely aetiology of the cerebral palsy. Characteristics of a subgroup of children with intrapartum hypoxia will also be described.

4.4.1 Description of the Maternal Sample

Maternal age at delivery ranged from 16 to 44 years with a mean age of 30 years (SD 5.9). Four (4%) of the mothers in this cohort were under 20 years and 26 (26%) were over 35 years, with 7 of the mothers being over 40 years old. Forty one (41%) of mothers were nulliparous and 59 (59%) were multiparous. The number of previous births experienced by the women ranged from 0 to 9 with a median of 1 (IQR: 0-2). Sixteen (16%) of the mothers had 4 or more previous births. Maternal disorders identified in the literature as being associated with cerebral palsy were present in 33% (n=33) of mothers during the pregnancy. Among those disorders were hypothyroidism (n=2), epilepsy (n=4), pre-eclampsia (n=12), renal disease (n=1), coagulopathies (n=1), diabetes (n=4) and hypertension (n=9). Three (3%) of the mothers had received fertility treatment. Five (5%) mothers had a confirmed antenatal infection.

Onset of labour was spontaneous for 64% of mothers. The modes of birth experienced were; 55% spontaneous vaginal, 17% instrumental and 28% caesarean section. Of the 28 caesarean sections, 18% (n=5) were elective and 82% (n=23) emergency.

The duration of rupture of membranes ranged from 0 to 504 hours with a median of 4 hours (IQR: 1.17-8.13hrs). In 5% (n=5) of cases, duration of rupture of membranes was greater than 24 hours (range 28-504hrs) and so considered prolonged according to the definition of prolonged rupture of membranes (PROM) at that time. The gestational age of the babies of mothers with PROM ranged from 24 to 39 weeks at birth. Three (60%) of the 5 babies of women with PROM had a subsequent
neonatal sepsis documented. None of those 5 PROM mothers had any record of pyrexia in labour or antenatal infection. Forty-nine (49%) of placentas were sent for histology. Of those 22 (45%) had placental pathologies reported. Thirteen placentas (59%) were noted to have infarcts, 3 (13%) had evidence of histological chorioamnionitis and 6 (26%) had retroplacental clots noted.

There were a number of significant events experienced by mothers during labour that are also recognised in the literature as being associated with cerebral palsy. Among those associated events were; breech position at birth 14% (n=14), persistent occipitoposterior position 1% (n=1), shoulder dystocia 2% (n=2), meconium stained liquor 17% (n=17) and pyrexia in labour 11% (n=11). Fourteen percent (n=14) of the mothers had experienced an antepartum haemorrhage.

Many of the labours complicated by these significant events manifested additional cerebral palsy risk factors. Of note, 5 (36%) of the breech babies had an Apgar score below 6 at 1 minute and 2 (14%) had score below 6 persisting at 5 minutes. Three (21%) of the breech babies had a metabolic acidosis at birth. Among the 17 babies with meconium stained amniotic fluid, 10 (59%) of them had an Apgar score below 6 at 1 minute and 7 (41%) had an Apgar below 6 at 5 minutes. Four (23%) of the 17 had a metabolic acidosis documented and went on to subsequently have a moderate (1 case) or severe (3 cases) encephalopathy. Nine (53%) of the 17 cases experienced neonatal seizures and 8 (47%) experienced meconium aspiration syndrome. Hypertension and pre-eclampsia are risk factors for abruptio and two of the mothers (14%) who experienced abruptio had pregnancy induced hypertension and 3 (21%) had pre-eclampsia. Ten of the 14 mothers (71%) with abruptio in this study delivered premature babies. Eleven (11%) of the mothers in the cohort had a pyrexia in labour; four (36%) of whom had a documented antenatal infection and 2 (18%) of whom had a preterm baby. Five (45%) of the 11 babies born to mothers with an intrapartum pyrexia were preterm. Two (33%) of the 6 term babies born following pyrexia in labour had a metabolic acidosis at birth and three (50%) went on to develop severe encephalopathy. Seven of the 11 (64%) placentas were examined for pathology and 2 (18%) were found to have inflammation consistent with chorioamnionitis. This illustrates the often co-existing risk factors when studying cerebral palsy.

Cardiotocographs (CTG) were recorded during labour for 98% (n=98) of the mothers. Of those recorded CTGs, 58% (n=58) were normal, 10% (n=10) suspicious and 30% (n=30) were pathological. Table 4.1 outlines the details of the maternal sample.
Table 4.1: Details of the Maternal Sample

<table>
<thead>
<tr>
<th>Maternal Characteristics</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mothers Age</strong></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>30 years</td>
</tr>
<tr>
<td>Standard deviation</td>
<td>5.9 years</td>
</tr>
<tr>
<td>Range</td>
<td>16-44 years</td>
</tr>
<tr>
<td><strong>Number of Previous Births</strong></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>1.0 births</td>
</tr>
<tr>
<td>Range</td>
<td>0-9 births</td>
</tr>
<tr>
<td><strong>Parity</strong></td>
<td></td>
</tr>
<tr>
<td>Parity = 0 (n, %)</td>
<td>41 (41%)</td>
</tr>
<tr>
<td>parity = 1 (n, %)</td>
<td>26 (26%)</td>
</tr>
<tr>
<td>parity = 2 (n, %)</td>
<td>13 (13%)</td>
</tr>
<tr>
<td>parity = 3 (n, %)</td>
<td>4 (4%)</td>
</tr>
<tr>
<td>parity ≥ 4 (n, %)</td>
<td>16 (16%)</td>
</tr>
<tr>
<td><strong>Mode of Birth</strong></td>
<td></td>
</tr>
<tr>
<td>Spontaneous Vaginal (n, %)</td>
<td>55 (55%)</td>
</tr>
<tr>
<td>Instrumental (n, %)</td>
<td>17 (17%)</td>
</tr>
<tr>
<td>Caesarean section (n, %)</td>
<td>28 (28%)</td>
</tr>
<tr>
<td><strong>Duration of Rupture of Membranes</strong></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>4 hours</td>
</tr>
<tr>
<td>Percentiles</td>
<td></td>
</tr>
<tr>
<td>25th</td>
<td>01:17 hours</td>
</tr>
<tr>
<td>50th</td>
<td>04:00 hours</td>
</tr>
<tr>
<td>75th</td>
<td>08:13 hours</td>
</tr>
<tr>
<td>Range</td>
<td>0-504 hours</td>
</tr>
<tr>
<td><strong>Significant Intrapartum Event</strong></td>
<td></td>
</tr>
<tr>
<td>Breech position (n, %)</td>
<td>14 (14%)</td>
</tr>
<tr>
<td>Persistent OP (n, %)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Shoulder dystocia (n, %)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Pyrexia in labour (n, %)</td>
<td>11 (11%)</td>
</tr>
<tr>
<td>Meconium liquor (n, %)</td>
<td>17 (17%)</td>
</tr>
<tr>
<td>Antepartum haemorrhage (n, %)</td>
<td>14 (14%)</td>
</tr>
<tr>
<td>Pathological CTG (n, %)</td>
<td>30 (30%)</td>
</tr>
<tr>
<td><strong>Labour CTG</strong></td>
<td></td>
</tr>
<tr>
<td>Normal (n, %)</td>
<td>58 (58%)</td>
</tr>
<tr>
<td>Suspicious (n, %)</td>
<td>10 (10%)</td>
</tr>
<tr>
<td>Pathological (n, %)</td>
<td>30 (30%)</td>
</tr>
<tr>
<td>Not recorded (n, %)</td>
<td>2 (2%)</td>
</tr>
</tbody>
</table>

The association between risk factors and outcomes were explored for maternal data. The risk ratios (RR) and confidence intervals (95%CI) are shown below in table 4.2.
### Table 4.2: Associations between risk factors and outcomes

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Neonatal Encephalopathy</th>
<th>Metabolic Acidosis</th>
<th>5min Apgar &lt; 6</th>
<th>Abnormal CTG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antenatal infection + PROM</td>
<td>0.50 [0.07-3.36]</td>
<td>1.20 [0.32-4.51]</td>
<td>1.38 [0.36-5.28]</td>
<td>1.50 [0.85-2.64]</td>
</tr>
<tr>
<td>Maternal pyrexia in labour</td>
<td>1.87 [0.63-5.54]</td>
<td>1.73 [0.59-5.10]</td>
<td>1.24 [0.32-4.80]</td>
<td>0.99 [0.38-2.67]</td>
</tr>
<tr>
<td>Placental abruption</td>
<td>1.89 [0.72-4.98]</td>
<td>5.46 [2.54-11.76]</td>
<td>1.54 [0.50-4.76]</td>
<td>1.78 [1.10-2.98]</td>
</tr>
<tr>
<td>Instrumental birth</td>
<td>2.85 [1.32-6.17]</td>
<td>1.50 [0.56-4.05]</td>
<td>1.2 [0.39-3.86]</td>
<td>1.63 [1.0-2.66]</td>
</tr>
<tr>
<td>Emergency C-section</td>
<td>0.89 [0.33-2.43]</td>
<td>1.83 [0.76-4.40]</td>
<td>1.22 [0.43-3.46]</td>
<td>3.35 [2.22-5.04]</td>
</tr>
</tbody>
</table>

Risk ratios (RR) and confidence intervals (95%CI)

#### 4.4.2 Birth Details of the Children

Details of the births of the 100 children were analysed. Singleton births accounted for 89% (n=89) and multiple births for 11% (n=11) of the cohort. The gestational age of the cohort ranged from 24 to 42 weeks with a median of 39 weeks (IQR: 31-40 weeks). Overall 61% (n=61) of children were born at term (>37 weeks gestation). Thirty-nine percent (n=39) of the cohort was born prematurely (≤ 37 weeks gestation). Eleven percent (n=11) were born extremely preterm (< 28 weeks gestation), 18% (n=18) very preterm (28-32 weeks) and 10% (n=10) moderately preterm (33-37 weeks). Table 4.3 outlines the distribution of gestational age in weeks in the cohort.

### Table 4.3: Gestational age profile of the cohort

<table>
<thead>
<tr>
<th>Gestational age</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 28 weeks gestation</td>
<td>11 (11)</td>
</tr>
<tr>
<td>28-32 weeks gestation</td>
<td>18 (18)</td>
</tr>
<tr>
<td>33-37 weeks gestation</td>
<td>10 (10)</td>
</tr>
<tr>
<td>&gt; 37 weeks gestation</td>
<td>61 (61)</td>
</tr>
</tbody>
</table>

The birth weights of the cohort ranged from 780 grams to 4990 grams with a median of 3055grams (IQR:1600-3460grms). The majority (60%) of the babies were of normal birth weight (>2500grams). Low birth weight babies (<2500grams) accounted for 40% (n=40) of the cohort. Eleven percent (n=11) of the cohort were born extremely low birth weight (<1,000 grams), 12% (n=12) very low birth weight (1000-1499 grams) and 17% (n=17) moderately low birth weight (1500-2499 grams). Intrauterine growth restriction is strongly correlated with cerebral palsy. Eighteen (18%) of the cohort had a birth weight that was equal to or less than 10th percentile with 13% having a birth weight less than the 5th percentile. Table 4.4 outlines the distribution of birth weight in grams in the cohort.
There was an excess of boys among the cohort. There were 63 boys and 37 girls giving a male: female ratio of 1.7:1. The birth characteristics of the cohort are outlined below in Table 4.5.

Table 4.5: Birth Characteristics of the Cohort

<table>
<thead>
<tr>
<th>Birth characteristic</th>
<th>Birth characteristic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>63 (63)</td>
</tr>
<tr>
<td>Male: n (%)</td>
<td>Female: n (%)</td>
</tr>
<tr>
<td>63 (63)</td>
<td>37 (37)</td>
</tr>
<tr>
<td>Gestational age (in weeks)</td>
<td>39 weeks</td>
</tr>
<tr>
<td>Median</td>
<td>Percentiles</td>
</tr>
<tr>
<td>25th</td>
<td>31 weeks</td>
</tr>
<tr>
<td>50th</td>
<td>39 weeks</td>
</tr>
<tr>
<td>75th</td>
<td>40 weeks</td>
</tr>
<tr>
<td>Range</td>
<td>24-42</td>
</tr>
<tr>
<td>Birth Weight (in grams)</td>
<td>3055 grams</td>
</tr>
<tr>
<td>Median</td>
<td>Percentiles</td>
</tr>
<tr>
<td>25th</td>
<td>1600 grams</td>
</tr>
<tr>
<td>50th</td>
<td>3055 grams</td>
</tr>
<tr>
<td>75th</td>
<td>3460 grams</td>
</tr>
<tr>
<td>Range</td>
<td>780-4990</td>
</tr>
</tbody>
</table>

Apgar scores were available at 1 and 5 minutes for all 100% (n=100) of cases but missing at 10 minutes for 65% (n=65) of cases. The range of 1-minute Apgar scores was 0 to 10 with a median of 7. The range of 5-minute Apgar scores was 0 to 10 with a median of 9. Ten minute Apgar scores were only available for 35% (n=35) of the cohort. The range of 10-minute Apgar scores was 4 to 10 with a median of 9. Table 4.6 outlines the distribution of Apgar scores in the cohort.

Table 4.6: Distribution of Apgar scores in the cohort

<table>
<thead>
<tr>
<th>Apgar Score</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 minute Apgar (n=100)</td>
<td></td>
</tr>
<tr>
<td>0-3</td>
<td>12 (12)</td>
</tr>
<tr>
<td>4-6</td>
<td>23 (23)</td>
</tr>
<tr>
<td>7-10</td>
<td>65 (65)</td>
</tr>
<tr>
<td>Median</td>
<td>7</td>
</tr>
<tr>
<td>Range</td>
<td>0-10</td>
</tr>
<tr>
<td>5 minute Apgar (n=100)</td>
<td></td>
</tr>
<tr>
<td>0-3</td>
<td>5 (5)</td>
</tr>
<tr>
<td>4-6</td>
<td>10 (10)</td>
</tr>
<tr>
<td>7-10</td>
<td>85 (85)</td>
</tr>
<tr>
<td>Median</td>
<td>9</td>
</tr>
<tr>
<td>Range</td>
<td>0-10</td>
</tr>
<tr>
<td>10 minute Apgar (n=35)</td>
<td></td>
</tr>
<tr>
<td>0-3</td>
<td>0 (0)</td>
</tr>
<tr>
<td>4-6</td>
<td>4 (12)</td>
</tr>
<tr>
<td>7-10</td>
<td>31 (88)</td>
</tr>
<tr>
<td>Median</td>
<td>9</td>
</tr>
<tr>
<td>Range</td>
<td>4-10</td>
</tr>
</tbody>
</table>
The association between Apgar scores and adverse outcomes were explored. The risk ratios and 95% confidence intervals (RR [95%CI]) for the associations are shown below in table 4.7.

### Table 4.7: Association between Apgar scores and adverse outcomes

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Outcome</th>
<th>RR [95%CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apgar &lt;6 @ 5 min</td>
<td>Abnormal CTG</td>
<td>2.15 [1.41-3.29]</td>
</tr>
<tr>
<td>Apgar &lt;6 @ 5 min</td>
<td>Metabolic Acidosis</td>
<td>6.38 [2.93-13.88]</td>
</tr>
<tr>
<td>Apgar &lt;6 @ 5 min</td>
<td>Seizures</td>
<td>10.39 [4.53-23.81]</td>
</tr>
<tr>
<td>Apgar &lt;6 @ 5 min</td>
<td>Neonatal Encephalopathy</td>
<td>7.79 [3.77-16.12]</td>
</tr>
<tr>
<td>Apgar &lt;3 @ 5 min</td>
<td>Abnormal CTG</td>
<td>2.48 [1.74-3.54]</td>
</tr>
<tr>
<td>Apgar &lt;3 @ 5 min</td>
<td>Metabolic Acidosis</td>
<td>4.71 [1.72-9.66]</td>
</tr>
<tr>
<td>Apgar &lt;3 @ 5 min</td>
<td>Seizures</td>
<td>7.04 [3.98-12.46]</td>
</tr>
<tr>
<td>Apgar &lt;3 @ 5 min</td>
<td>Neonatal Encephalopathy</td>
<td>7.04 [3.98-12.46]</td>
</tr>
</tbody>
</table>

Sixty-six percent (n=66) of the babies received some resuscitation at birth. The level of resuscitation required varied among the cohort and is outlined below in Table 4.8. Of the 66 babies who did require some form of resuscitation, the most common forms were suction 66% (n=66) and facial oxygen 65% (n=65). A very small proportion of babies required chest compressions (4%, n=4) and resuscitation drugs (2%, n=2).

### Table 4.8: Resuscitation required at birth

<table>
<thead>
<tr>
<th>Resuscitation at birth</th>
<th>N=100 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suction</td>
<td>66 (66)</td>
</tr>
<tr>
<td>Oxygen</td>
<td>65 (65)</td>
</tr>
<tr>
<td>Bag and mask ventilation</td>
<td>44 (44)</td>
</tr>
<tr>
<td>Intubation</td>
<td>35 (35)</td>
</tr>
<tr>
<td>Chest compressions</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Resuscitation drugs</td>
<td>2 (2)</td>
</tr>
</tbody>
</table>

*Note: categories are not mutually exclusive

The acid-base status at birth or shortly thereafter was available for 58% (n=58) of all babies. Forty-two percent (n=42) of the babies had no recorded analysis of acid-base status. Thirty-eight percent (n=38) of the babies had cord blood samples taken at birth for analysis. The remaining 20% (n=20) of blood gases were taken in the neonatal unit.

The pH measurements available ranged from 6.64 to 7.48 with a median of 7.2 (IQR: 6.9-7.28). The Base Deficit (BD) measurements ranged from 1 to 19 with a median of 9 (IQR: 6-15). Evidence of metabolic acidosis is considered to be present if the pH < 7 and the BD ≥ 12 mmols. Seventeen percent (n=17) of the cohort had a metabolic acidosis diagnosed on analysis of acid-base status.

Of the 17 babies with a documented metabolic acidosis, 9 babies (53%) had a diagnosis of severe encephalopathy, 7 babies (41%) had no encephalopathy recorded and 1 baby (6%) had moderate encephalopathy. Table 4.9 outlines details of the distribution of neonatal encephalopathy in the babies with documented metabolic acidosis.

### Table 4.9: Distribution of neonatal encephalopathy in the babies with documented metabolic acidosis

<table>
<thead>
<tr>
<th>Neonatal Encephalopathy</th>
<th>Metabolic Acidosis Present (n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None n (%)</td>
<td>7 (41)</td>
</tr>
<tr>
<td>Moderate n (%)</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Severe n (%)</td>
<td>9 (53)</td>
</tr>
<tr>
<td>Total n (%)</td>
<td>17 (100)</td>
</tr>
</tbody>
</table>
There are 19 documented cases of neonatal encephalopathy in the overall cohort of babies, 3 of whom were born to women over 35 years old. Table 4.10 outlines details of the incidence of mild, moderate and severe neonatal encephalopathy in both term and preterm babies in the cohort. Eighteen of the 19 (95%) cases of encephalopathy were in term babies. Among those term babies, 11% (n=2) had mild encephalopathy, 17% (n=3) had a moderate encephalopathy and 72% (n=13) had a severe encephalopathy. One preterm baby had a diagnosis of severe encephalopathy recorded in the medical records.

Table 4.10: Incidence of neonatal encephalopathy stratified by gestational age

<table>
<thead>
<tr>
<th>Gestation at birth</th>
<th>No</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Term</td>
<td>43 (43)</td>
<td>2 (2)</td>
<td>3 (3)</td>
<td>13 (13)</td>
<td>61 (61)</td>
</tr>
<tr>
<td>Preterm</td>
<td>38 (38)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (1)</td>
<td>39 (39)</td>
</tr>
<tr>
<td>Total</td>
<td>81 (81)</td>
<td>2 (2)</td>
<td>3 (3)</td>
<td>14 (14)</td>
<td>100 (100)</td>
</tr>
</tbody>
</table>

Sixty-three percent (n=63) of the babies were admitted to the neonatal unit following birth. The length of stay in the neonatal unit ranged from 5 to 180 days and the mean and median were 48 and 35 respectively. The longer lengths of stay were experienced by the preterm babies. Sixty percent (n=38) of those admitted to neonatal care were preterm (≤37 weeks gestation) and 40% (n=25) were term (> 37 weeks gestation). It is recognised that there are a number of neonatal illnesses associated with cerebral palsy. A number of those recognised neonatal illnesses were encountered within the cohort of 63 babies admitted to the neonatal unit. Table 4.11 lists the distribution of neonatal illnesses in the cohort of 63 babies admitted to the neonatal unit.

Table 4.11: Distribution of neonatal illnesses in the cohort of babies admitted to the neonatal unit

<table>
<thead>
<tr>
<th>Neonatal Illness</th>
<th>N=63 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumothorax</td>
<td>5 (8)</td>
</tr>
<tr>
<td>Hypoglycaemia</td>
<td>7 (11)</td>
</tr>
<tr>
<td>Meconium Aspiration</td>
<td>8 (13)</td>
</tr>
<tr>
<td>Necrotising Enterocolitis</td>
<td>10 (16)</td>
</tr>
<tr>
<td>Patent Ductus Arteriosus</td>
<td>12 (19)</td>
</tr>
<tr>
<td>Thrombocytopenia/ Coagulopathy</td>
<td>15 (24)</td>
</tr>
<tr>
<td>Neonatal Seizures</td>
<td>17 (27)</td>
</tr>
<tr>
<td>Chronic Lung Disease</td>
<td>20 (32)</td>
</tr>
<tr>
<td>Neonatal Sepsis</td>
<td>24 (38)</td>
</tr>
<tr>
<td>Blood Transfusion</td>
<td>27 (43)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>32 (51)</td>
</tr>
<tr>
<td>Prolonged ventilation</td>
<td>39 (62)</td>
</tr>
</tbody>
</table>

*Note: categories are not mutually exclusive

The neonatal illnesses experienced differ for term and preterm babies. Risk ratios (RR) and 95% confidence intervals (95% CI) are shown in table 4.12 for the differences in proportions of illnesses between the term and preterm babies.
Table 4.12: Differences in proportions of neonatal illnesses by gestational age

<table>
<thead>
<tr>
<th>Neonatal Illness</th>
<th>Preterm</th>
<th>Term</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumothorax</td>
<td>3 (60%)</td>
<td>2 (40%)</td>
<td>0.99 [0.18-5.49]</td>
</tr>
<tr>
<td>Hypoglycaemia</td>
<td>3 (43%)</td>
<td>4 (57%)</td>
<td>0.49 [0.12-2.02]</td>
</tr>
<tr>
<td>Meconium Aspiration</td>
<td>0</td>
<td>8 (100%)</td>
<td>N/A</td>
</tr>
<tr>
<td>Necrotising Enterocolitis</td>
<td>10 (100%)</td>
<td>0</td>
<td>N/A</td>
</tr>
<tr>
<td>Patent Ductus Arteriosus</td>
<td>11 (92%)</td>
<td>1 (8%)</td>
<td>7.24 [1.00-52.62]</td>
</tr>
<tr>
<td>Thrombocytopenia/Coagulopathy</td>
<td>8 (53%)</td>
<td>7 (47%)</td>
<td>0.75 [0.31-1.18]</td>
</tr>
<tr>
<td>Neonatal Seizures</td>
<td>1 (6%)</td>
<td>16 (94%)</td>
<td>0.04 [0.01-0.29]</td>
</tr>
<tr>
<td>Chronic Lung Disease</td>
<td>20 (100%)</td>
<td>0</td>
<td>N/A</td>
</tr>
<tr>
<td>Neonatal Sepsis</td>
<td>23 (95%)</td>
<td>1 (5%)</td>
<td>15.13 [2.18-103.03]</td>
</tr>
<tr>
<td>Blood Transfusion</td>
<td>26 (96%)</td>
<td>1 (4%)</td>
<td>17.11 [2.48-118.14]</td>
</tr>
<tr>
<td>Hypotension</td>
<td>25 (78%)</td>
<td>7 (22%)</td>
<td>2.35 [1.20-4.59]</td>
</tr>
<tr>
<td>Prolonged Ventilation</td>
<td>29 (76%)</td>
<td>10 (24%)</td>
<td>1.91 [1.14-3.18]</td>
</tr>
</tbody>
</table>

N/A: Not appropriate because there are zero episodes of the outcome of interest in one of the groups.

4.4.3 Cerebral Palsy Subtypes

The cohort were further analysed to determine the distribution of cerebral palsy subtypes. In keeping with SCPE guidelines three clinical subtypes of cerebral palsy were identified in the cohort; spastic, dyskinetic and ataxic. The cerebral palsy subtype was further classified into hemiplegia, quadriplegia and diplegia depending on the number of limbs affected. Spasticity was the predominant subtype affecting 84% (n=84) of cases. Of the 100 children in the cohort 34% (n=34) have a spastic hemiplegia, 26% (n=26) a spastic diplegia, 24% (n=24) a spastic quadriplegia, 10% (n=10) a dyskinesia and 6% (n=6) of children have an ataxic cerebral palsy. Figure 4.2 outlines details regarding the distribution of cerebral palsy subtypes found in the cohort.

Figure 4.2 The distribution of cerebral palsy subtypes in the cohort
The distribution of cerebral palsy subtypes varies according to gestational age. Table 4.13 outlines details regarding the distribution of subtypes by gestational age.

Table 4.13: Distribution of the Cerebral Palsy Subtypes by gestation in the cohort

<table>
<thead>
<tr>
<th>SCPE CP Classification</th>
<th>Gestation at birth</th>
<th></th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Term n (%)</td>
<td>Preterm n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Spastic Hemiplegia</td>
<td>29 (29)</td>
<td>5 (5)</td>
<td>34 (34)</td>
</tr>
<tr>
<td>Spastic Quadriplegia</td>
<td>13 (13)</td>
<td>11 (11)</td>
<td>24 (24)</td>
</tr>
<tr>
<td>Spastic Dipelegia</td>
<td>8 (8)</td>
<td>18 (18)</td>
<td>26 (26)</td>
</tr>
<tr>
<td>Dyskinetic CP</td>
<td>6 (6)</td>
<td>4 (4)</td>
<td>10 (10)</td>
</tr>
<tr>
<td>Ataxic CP</td>
<td>5 (5)</td>
<td>1 (1)</td>
<td>6 (6)</td>
</tr>
<tr>
<td>Total</td>
<td>61 (61)</td>
<td>39 (39)</td>
<td>100 (100)</td>
</tr>
</tbody>
</table>

The cerebral palsy subtypes differ for term and preterm babies. Risk ratios (RR) and 95% confidence intervals (95% CI) are shown in Table 4.14 for the differences in proportions of cerebral palsy subtype between the term and preterm babies.

Table 4.14: Differences in proportions of cerebral palsy subtype between the term and preterm babies

<table>
<thead>
<tr>
<th>CP subtype n (%)</th>
<th>Term n (%)</th>
<th>Preterm n (%)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spastic Hemiplegia 34 (34)</td>
<td>29 (85)</td>
<td>5 (15)</td>
<td>3.71 [1.57, 8.76]</td>
</tr>
<tr>
<td>Spastic Quadriplegia 24 (24)</td>
<td>13 (54)</td>
<td>11 (46)</td>
<td>0.76 [0.38, 1.51]</td>
</tr>
<tr>
<td>Spastic Dipelegia 26 (26)</td>
<td>8 (31)</td>
<td>18 (69)</td>
<td>0.28 [0.14, 0.59]</td>
</tr>
<tr>
<td>Dyskinetic CP 10 (10)</td>
<td>6 (60)</td>
<td>4 (40)</td>
<td>0.96 [0.29, 3.18]</td>
</tr>
<tr>
<td>Ataxic CP 6 (6)</td>
<td>5 (83)</td>
<td>1 (17)</td>
<td>3.2 [0.39, 26.34]</td>
</tr>
</tbody>
</table>

4.4.4 Co-morbidity

Many children with cerebral palsy have additional impairments other than the motor impairments that compound their condition. Recognised additional impairments include visual, hearing, intellectual and feeding difficulties as well as seizures.

Forty-nine percent (n=49) of the children had experienced seizure activity and for 44% (n=44) of children, seizure activity is still an on-going issue. In general, children with active seizures had the most severe forms of CP. Of the 44 children with on-going seizure activity, 66% (n=29) had a severe intellectual impairment and 43% (n=19) had the spastic quadriplegic subtype.

Feeding ability is an indication of functional ability. Fifty-six percent (n=56) of children had difficulties with self-feeding. Thirty-eight percent (n=21) of those experienced mild difficulties but 63% (n=35) have significant difficulty with self-feeding. The majority of children with significant feeding difficulties (41%, n=41) were in the spastic quadriplegic subgroup.

The presence of co-morbidities and the severity of those co-morbidities among the cohort are presented below in table 4.15
Table 4.15: Frequency of co-morbidities in the cohort

<table>
<thead>
<tr>
<th>Associated Impairments*</th>
<th>None n (%)</th>
<th>Mild n (%)</th>
<th>Moderate n (%)</th>
<th>Severe n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Walking Impairment</td>
<td>16 (16)</td>
<td>33 (33)</td>
<td>16 (16)</td>
<td>35 (35)</td>
</tr>
<tr>
<td>Visual Impairment</td>
<td>80 (80)</td>
<td>3 (3)</td>
<td>3 (3)</td>
<td>14 (14)</td>
</tr>
<tr>
<td>Hearing Impairment</td>
<td>87 (87)</td>
<td></td>
<td>8 (8)</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Intellectual Impairment</td>
<td>38 (38)</td>
<td>11 (11)</td>
<td>12 (11)</td>
<td>39 (39)</td>
</tr>
<tr>
<td>Feeding Difficulty</td>
<td>44 (44)</td>
<td>21 (21)</td>
<td>6 (6)</td>
<td>29 (29)</td>
</tr>
<tr>
<td>Seizures</td>
<td>51 (51)</td>
<td>15 (15)</td>
<td></td>
<td>44 (44)</td>
</tr>
</tbody>
</table>

*Categories are not mutually exclusive

The likelihood and severity of associated impairments increases with increasing severity of motor impairment. The distribution of severe co-morbidities across cerebral palsy subtypes is outlined below in Table 4.16.

Table 4.16: Frequencies of severe co-morbidities distributed by cerebral palsy subtype

<table>
<thead>
<tr>
<th>Severe co-morbidities</th>
<th>Spastic Hemiplegia (n=34)</th>
<th>Spastic Quadruplegia (n=24)</th>
<th>Spastic Diplegia (n=26)</th>
<th>Dyskinetic CP (n=10)</th>
<th>Ataxic CP (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe Visual Loss n (%)</td>
<td>0</td>
<td>9 (37)</td>
<td>2 (8)</td>
<td>0</td>
<td>3 (50)</td>
</tr>
<tr>
<td>Severe Hearing Loss n (%)</td>
<td>2 (6)</td>
<td>0</td>
<td>2 (8)</td>
<td>1 (10)</td>
<td>0</td>
</tr>
<tr>
<td>Severe/profound Intellectual Impairment n (%)</td>
<td>3 (9)</td>
<td>23 (96)</td>
<td>6 (23)</td>
<td>2 (20)</td>
<td>5 (83)</td>
</tr>
<tr>
<td>Severe Feeding problems n (%)</td>
<td>0</td>
<td>22 (92)</td>
<td>1 (4)</td>
<td>4 (40)</td>
<td>2 (33)</td>
</tr>
<tr>
<td>Active Seizures n (%)</td>
<td>10 (29)</td>
<td>19 (79)</td>
<td>7 (27)</td>
<td>3 (30)</td>
<td>5 (83)</td>
</tr>
</tbody>
</table>

Intellectual ability, walking ability and the occurrence of epilepsy are highly dependent on cerebral palsy subtype. The association between cerebral palsy subtype and severe co-morbidities are shown below in table 4.17.

Table 4.17: Association between cerebral palsy subtype and severe co-morbidities

<table>
<thead>
<tr>
<th>Cerebral Palsy subtype</th>
<th>Unable to walk</th>
<th>Outcome RR [95%CI]</th>
<th>Epilepsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spastic Hemiplegia</td>
<td>0.08 [0.02-0.31]</td>
<td>0.16 [0.05-0.49]</td>
<td>0.57 [0.32-1.01]</td>
</tr>
<tr>
<td>Spastic Quadriplegia</td>
<td>2.74 [2.02-3.72]</td>
<td>4.55 [2.92-7.09]</td>
<td>2.41 [1.64-3.52]</td>
</tr>
<tr>
<td>Spastic Diplegia</td>
<td>1.93 [0.73-5.08]</td>
<td>1.17 [0.53-2.59]</td>
<td>0.95 [0.45-2.01]</td>
</tr>
</tbody>
</table>

Thirty five percent (n=35) of the cohort had no independent walking ability and 39% (n=39) had been diagnosed with a profound or severe intellectual impairment. The SCPE criteria define the most severe cases of cerebral palsy as those cases unable to walk and with a severe intellectual impairment. Twenty-eight percent (n=28) of the 100 cases in this cohort were found to have a combination of those two severe impairments, the majority (82%) of which occurred in the children affected by spastic quadriplegic cerebral palsy. This cerebral palsy subtype is accepted to be the most severe form. Table 4.18 shows the distribution of the combination of the two most severe impairments across the cerebral palsy subtypes.

84
Table 4.18: Severe cases of CP stratified by cerebral palsy subtype

<table>
<thead>
<tr>
<th>Combined Severe Impairments</th>
<th>SCPE Cerebral Palsy Classification</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Profound/Severe intellectual impairment Plus No independent walking (n= 28)</td>
<td>Spastic Quadriplegia</td>
<td>23 (82.5%)</td>
</tr>
<tr>
<td></td>
<td>Spastic Diplegia</td>
<td>2 (7%)</td>
</tr>
<tr>
<td></td>
<td>Dyskinetic CP</td>
<td>2 (7%)</td>
</tr>
<tr>
<td></td>
<td>Ataxic CP</td>
<td>1 (3.5%)</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>28 (100%)</td>
</tr>
</tbody>
</table>

4.4.5 Aetiology

The children in the cohort were also classified by the aetiology of their cerebral palsy. Aetiology, classified by likely time of origin, is based on clinical criteria, neuro-imaging information and expert opinion. Cases were classified into antenatal (including vascular and genetic), perinatal term, preterm (including perinatal and neonatal), neonatal (including post-neonatal) and unclassifiable. The aetiology by likely time of origin is outlined below in Table 4.19.

Table 4.19: Aetiology by likely time of origin

<table>
<thead>
<tr>
<th>Aetiology</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antenatal (including vascular and genetic)</td>
<td>38 (38)</td>
</tr>
<tr>
<td>Perinatal (Term only)</td>
<td>15 (15)</td>
</tr>
<tr>
<td>Preterm (including perinatal and neonatal)</td>
<td>28 (28)</td>
</tr>
<tr>
<td>Neonatal and post neonatal</td>
<td>6 (6)</td>
</tr>
<tr>
<td>Unclassifiable</td>
<td>13 (13)</td>
</tr>
<tr>
<td>Total</td>
<td>100 (100)</td>
</tr>
</tbody>
</table>

The aetiology was considered unclassifiable in 13(13%) of cases. Of the 13 cases where the likely aetiology was unknown, one was premature (29 weeks gestation) and spent 76 days in the neonatal unit but had a normal cerebral scan. The other 12 children were full term (38-42 weeks gestation) and were all in good condition at birth. Of the 13 unclassifiable cases, 62% (n=8) have a spastic hemiplegia, 31% (n=4) a spastic diplegia and 7% (n=1) has a spastic quadriplegia.

An antenatal aetiology was identified in 38% (n=38) of cases. Seventy-six percent (n=29) of the antenatal cases were term and 24% (n=9) were preterm. Cerebral malformation and vascular insults were the predominant antenatal associated factors. Genetic conditions, congenital abnormalities and cytomegalovirus were also present in the antenatal cases. Of the 38 cases with an antenatal aetiology, 42% (n=16) have a spastic hemiplegia, 16% (n=6) a spastic diplegia, 21% (n=8) a spastic quadriplegia, 8% (n=3) dyskinesia and 13% (n=5) ataxic cerebral palsy. The associations between antenatal aetiology and outcomes were explored. The risk ratios and 95% confidence intervals for those associations are shown below in table 4.20.

Table 4.20: Associations between antenatal aetiology and outcomes

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Outcome RR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antenatal aetiology</td>
<td></td>
</tr>
<tr>
<td>Spastic hemiplegia</td>
<td>1.45 [0.85-2.49]</td>
</tr>
<tr>
<td>Severe walking impairment</td>
<td>0.75 [0.42-1.35]</td>
</tr>
<tr>
<td>Severe/profound IQ impairment</td>
<td>1.14 [0.69-1.86]</td>
</tr>
<tr>
<td>Seizures</td>
<td>1.19 [0.77-1.84]</td>
</tr>
<tr>
<td>Term gestation</td>
<td>1.38 [1.02-1.87]</td>
</tr>
</tbody>
</table>
Twenty-eight percent (n=28) of the cases were deemed to have an aetiology associated with prematurity. Those premature children experienced both perinatal and neonatal factors known to increase the risk of cerebral palsy. Among those associated factors were maternal pyrexia in labour, PROM, antepartum haemorrhage, placental pathology, low birth weight and significant neonatal illness. Seventy-eight percent (n=22) of the 28 premature children were found to have periventricular leukomalacia (PVL) and/or intraventricular haemorrhage (IVH) on cerebral imaging. Of the 28 cases with a premature aetiology, 14% (n=4) have a spastic hemiplegia, 50% (n=14) a spastic diplegia, 28% (n=8) a spastic quadriplegia, and 8% (n=2) a dyskinetic cerebral palsy. The associations between preterm aetiology and outcomes were explored. The risk ratios and 95% confidence intervals for those associations are shown below in table 4.21.

Table 4.21: Associations between preterm aetiology and outcomes

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Outcome RR [95%CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premature aetiology</td>
<td>Spastic diplegia</td>
</tr>
<tr>
<td></td>
<td>3.00 [1.59-5.66]</td>
</tr>
<tr>
<td></td>
<td>Severe walking impairment</td>
</tr>
<tr>
<td></td>
<td>1.52 [0.90-2.58]</td>
</tr>
<tr>
<td></td>
<td>Severe/profound IQ impairment</td>
</tr>
<tr>
<td></td>
<td>0.89 [0.50-1.57]</td>
</tr>
<tr>
<td></td>
<td>PVL &amp; IVH</td>
</tr>
<tr>
<td></td>
<td>29.57 [7.46-117.24]</td>
</tr>
<tr>
<td></td>
<td>Spastic quadriplegia</td>
</tr>
<tr>
<td></td>
<td>1.29 [0.62-2.66]</td>
</tr>
</tbody>
</table>

Neonatal and post neonatal factors other than illness due to prematurity were considered to be contributing factors in 6 (6%) of cases. Two of those children experienced significant infections in infancy. One had herpes simplex encephalitis at 22 months and one had TB meningitis at 19 months. One child suffered a post-operative anoxia after heart surgery, another a catastrophic intracranial bleed secondary to undiagnosed haemophilia, another bilateral infarcts after a prolonged supraventricular tachycardia (SVT) and the other an infarct consistent with neonatal stroke. Of the 6 cases with a neonatal and post neonatal aetiology, 50% (n=3) have a spastic hemiplegia, 17% (n=1) a spastic quadriplegia, 17% (n=1) a dyskinesia and 17% (n=1) an ataxic cerebral palsy.

A perinatal aetiology at term was assigned in 15 (15%) of cases in the cohort. Those perinatal cases are described in further detail later in section 4.4.6.

The timing of the aetiology of cerebral palsy will determine the resulting subtype of cerebral palsy. The aetiology stratified by cerebral palsy subtype for the 100 children in the cohort is outlined here in Table 4.22.
Table 4.22: Aetiology by SCPE cerebral palsy classification

<table>
<thead>
<tr>
<th>Aetiology</th>
<th>Spastic Hemiplegia</th>
<th>Spastic Quadriplegia</th>
<th>Spastic Diplegia</th>
<th>Dyskinesia</th>
<th>Ataxic</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antenatal including vascular and genetic</td>
<td>16</td>
<td>8</td>
<td>6</td>
<td>3</td>
<td>5</td>
<td>38</td>
</tr>
<tr>
<td>Preterm including perinatal and neonatal</td>
<td>4</td>
<td>8</td>
<td>14</td>
<td>2</td>
<td>0</td>
<td>28</td>
</tr>
<tr>
<td>Neonatal and post neonatal excluding preterm</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Unclassifiable</td>
<td>8</td>
<td>1</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>13</td>
</tr>
<tr>
<td>Perinatal</td>
<td>3</td>
<td>6</td>
<td>2</td>
<td>4</td>
<td>0</td>
<td>15</td>
</tr>
<tr>
<td>Total</td>
<td>34</td>
<td>24</td>
<td>26</td>
<td>10</td>
<td>6</td>
<td>100</td>
</tr>
</tbody>
</table>

4.4.6 Perinatal Aetiology

A perinatal aetiology was recorded for 15% (n=15) of cases in the cohort. The gestational age of these babies ranged from 37 to 41 weeks with a median of 40 weeks (mean 39.6, SD 1.2) The birth weights ranged from 2360 grams to 4990 grams with a median of 3460 grams (mean 3528, SD 683). All 15 cases (100%) experienced clinical signs of hypoxic ischaemic encephalopathy (HIE). Eighty seven percent of the babies (n=14) experienced seizures within 24 hours of birth and 67% (n=10) continued to experience active seizures at the time of data collection for this study. The 1-minute Apgar score for the babies with a perinatal aetiology ranged from 0 to 5 with a median of 2. Five-minute Apgar scores ranged from 0 to 7 with a median of 5. Ten minute Apgar scores were available for 86% (n=13) of cases and ranged from 3 to 9 with a median of 7. Blood gas analyses were recorded in all 15 cases. The first pH recorded ranged from 6.64 to 7.18 with a median of 6.9. The first base deficit recorded ranged from 13mmols to 19mmols with a median of 16mmols. Sixty-seven percent (n=10) of the cases had a pH <7.0 and a BD ≥ 12 and so were deemed to have evidence of metabolic acidosis.

The most common cerebral palsy subtype found among the 15 cases with a perinatal aetiology was spastic quadriplegia which was evident in 40% (n=6) of the 15 cases. Dyskinesia was present in 26% (n=4), spastic hemiplegia in 21% (n=3) and spastic diplegia in 13% (n=2) of cases. Sixty percent (n=9) of these 15 children were unable to walk and 60% (n=9) had a severe or profound intellectual impairment. The associations between perinatal aetiology and outcomes were explored. The risk ratios and 95% confidence intervals for those associations are shown below in table 4.23.

Table 4.23: Associations between perinatal aetiology and outcomes

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Outcome</th>
<th>RR [95%CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perinatal aetiology</td>
<td>Spastic quadriplegia</td>
<td>2.33 [1.17-4.64]</td>
</tr>
<tr>
<td></td>
<td>Dyskinesia</td>
<td>3.78 [1.21-11.81]</td>
</tr>
<tr>
<td></td>
<td>Severe walking impairment</td>
<td>1.74 [1.24-2.46]</td>
</tr>
<tr>
<td></td>
<td>Severe/profound IQ impairment</td>
<td>1.70 [1.03-2.81]</td>
</tr>
<tr>
<td></td>
<td>Epilepsy</td>
<td>1.67 [1.07-2.59]</td>
</tr>
</tbody>
</table>
The babies with a perinatal aetiology are described in detail below in Table 4.24.

<table>
<thead>
<tr>
<th>Case</th>
<th>Gestation</th>
<th>Apgar</th>
<th>First pH</th>
<th>First BD</th>
<th>HIE</th>
<th>Seizures in first 24 hrs</th>
<th>Sub-type</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>40</td>
<td>4/7/7&quot;</td>
<td>7.18</td>
<td>13</td>
<td>Yes</td>
<td>Yes</td>
<td>Dyskinetic</td>
</tr>
<tr>
<td>2</td>
<td>40</td>
<td>3/3/7&quot;</td>
<td>7.17</td>
<td>17</td>
<td>Yes</td>
<td>Yes</td>
<td>Spastic Dипlegia</td>
</tr>
<tr>
<td>3</td>
<td>40</td>
<td>0/5/7&quot;</td>
<td>6.87</td>
<td>16</td>
<td>Yes</td>
<td>Yes</td>
<td>Dyskinetic</td>
</tr>
<tr>
<td>4</td>
<td>41</td>
<td>2/5/8&quot;</td>
<td>6.84</td>
<td>13</td>
<td>Yes</td>
<td>Yes</td>
<td>Dyskinetic</td>
</tr>
<tr>
<td>5</td>
<td>41</td>
<td>5/7&quot;</td>
<td>7.02</td>
<td>16</td>
<td>Yes</td>
<td>Yes</td>
<td>Spastic Quadriplegia</td>
</tr>
<tr>
<td>6</td>
<td>40</td>
<td>4/5/8&quot;</td>
<td>7.08</td>
<td>13</td>
<td>Yes</td>
<td>Yes</td>
<td>Dyskinetic</td>
</tr>
<tr>
<td>7</td>
<td>41</td>
<td>3/3/5&quot;</td>
<td>6.9</td>
<td>18</td>
<td>Yes</td>
<td>Yes</td>
<td>Spastic Quadriplegia</td>
</tr>
<tr>
<td>8</td>
<td>41</td>
<td>4/6/7&quot;</td>
<td>6.9</td>
<td>18</td>
<td>Yes</td>
<td>No</td>
<td>Spastic Hemiplegia</td>
</tr>
<tr>
<td>9</td>
<td>39</td>
<td>2/3/3&quot;</td>
<td>7.01</td>
<td>16</td>
<td>Yes</td>
<td>Yes</td>
<td>Spastic Quadriplegia</td>
</tr>
<tr>
<td>10</td>
<td>38</td>
<td>4/6/8&quot;</td>
<td>6.8</td>
<td>16</td>
<td>Yes</td>
<td>Yes</td>
<td>Spastic Quadriplegia</td>
</tr>
<tr>
<td>11</td>
<td>38</td>
<td>1/7&quot;</td>
<td>6.7</td>
<td>17</td>
<td>Yes</td>
<td>Yes</td>
<td>Spastic Quadriplegia</td>
</tr>
<tr>
<td>12</td>
<td>40</td>
<td>2/4/31&quot;</td>
<td>6.9</td>
<td>17</td>
<td>Yes</td>
<td>Yes</td>
<td>Spastic Dипlegia</td>
</tr>
<tr>
<td>13</td>
<td>39</td>
<td>0/4/4&quot;</td>
<td>6.6</td>
<td>16</td>
<td>Yes</td>
<td>Yes</td>
<td>Spastic Hemiplegia</td>
</tr>
<tr>
<td>14</td>
<td>37</td>
<td>2/41&quot;</td>
<td>6.7</td>
<td>19</td>
<td>Yes</td>
<td>Yes</td>
<td>Spastic Quadriplegia</td>
</tr>
<tr>
<td>15</td>
<td>40</td>
<td>2/7/9&quot;</td>
<td>6.8</td>
<td>19</td>
<td>Yes</td>
<td>Yes</td>
<td>Spastic Quadriplegia</td>
</tr>
</tbody>
</table>

Cerebral imaging results were available for all 15 of the children with a perinatal aetiology. Sixty-six percent (n=10) of the children had magnetic resonance imaging (MRI) results in their medical records and 33% (n=5) had computerised axial topography (CT) recorded. The expert’s interpretations of the imaging findings of the 15 children as recorded in the medical records are summarised below in table 4.25.

<table>
<thead>
<tr>
<th>Case</th>
<th>Imaging report as documented in medical records</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Timing unclear but most likely perinatal/ asphyxia present at birth</td>
</tr>
<tr>
<td>2</td>
<td>CT results consistent with HIE and birth asphyxia</td>
</tr>
<tr>
<td>3</td>
<td>MRI consistent with acute perinatal HIE and birth asphyxia</td>
</tr>
<tr>
<td>4</td>
<td>Severe bilateral cerebral ischaemia consistent with HIE</td>
</tr>
<tr>
<td>5</td>
<td>Infarcts with ischaemic changes consistent with perinatal HIE and birth asphyxia</td>
</tr>
<tr>
<td>6</td>
<td>Infarcts with ischaemic changes consistent with perinatal HIE and birth asphyxia</td>
</tr>
<tr>
<td>7</td>
<td>Cerebral atrophy consistent with HIE and perinatal asphyxia</td>
</tr>
<tr>
<td>8</td>
<td>Diffuse low attenuation in both cerebral cortices consistent with perinatal asphyxia</td>
</tr>
<tr>
<td>9</td>
<td>Atrophy of right cerebral hemisphere, most likely HIE in origin</td>
</tr>
<tr>
<td>10</td>
<td>Findings consistent with ischaemia, probably HIE and birth asphyxia</td>
</tr>
<tr>
<td>11</td>
<td>Cerebral atrophy in frontal lobes consistent with perinatal HIE</td>
</tr>
<tr>
<td>12</td>
<td>HIE and birth asphyxia</td>
</tr>
<tr>
<td>13</td>
<td>Significant infarcts with ischaemic changes consistent with HIE</td>
</tr>
<tr>
<td>14</td>
<td>Frontal lobe atrophy most likely secondary to birth asphyxia</td>
</tr>
<tr>
<td>15</td>
<td>Significant infarcts with ischaemic changes, HIE and Birth asphyxia</td>
</tr>
</tbody>
</table>
4.5 Application of the objective criteria for the identification of acute intrapartum hypoxia

4.5.1 Application of the ACOG criteria

The study cohort were analysed to determine the proportion of cases meeting the objective criteria advocated in the literature for the identification of acute intrapartum hypoxia. Data analysis was undertaken to identify the presence of the nine criteria in the consensus statement (ACOG 2003). There are 4 essential criteria that identify severe hypoxia at birth and 5 suggestive criteria that, if present, together suggest intrapartum timing. At least 3 of the suggestive criteria have to be present to suggest an acute rather than chronic event. The objective criteria are divided into essential criteria and suggestive criteria as follows.

The objective criteria:

<table>
<thead>
<tr>
<th>Essential Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 pH &lt; 7.00 and base deficit ≥ 12 mmol/L</td>
</tr>
<tr>
<td>2 Onset of neonatal encephalopathy within 24 hours</td>
</tr>
<tr>
<td>3 CP of the spastic quadriplegic or dyskinetic type</td>
</tr>
<tr>
<td>4 Exclusion of other pathologies associated with CP</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Suggestive but non-specific to asphyxia insults</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Sentinel hypoxic event</td>
</tr>
<tr>
<td>2 Sudden sustained fetal bradycardia or other evidence of non-reassuring fetal status</td>
</tr>
<tr>
<td>3 Apgar scores of 0-3 beyond 5 minutes</td>
</tr>
<tr>
<td>4 Multisystem failure within 72 hours of birth</td>
</tr>
<tr>
<td>5 Evidence of acute nonfocal cerebral abnormality on early imaging</td>
</tr>
</tbody>
</table>

The essential criteria and the suggestive criteria are presented separately.

Essential Criteria:
Within the cohort, 6% (n=6) satisfied all 4 essential criteria. Eight percent (n=8) met at least 3 criteria, 5% (n=5) satisfied at least 2 criteria, 23% (n=23) at least one criteria and 58% (n=58) of the cohort did not meet any of the essential criteria. The 6 cases that satisfied all 4 essential criteria are found in the perinatal aetiology subgroup. The 8 cases that satisfied 3 of the essential criteria were also found in the perinatal aetiology group. Figure 4.3 illustrates these finding.

Suggestive Criteria:
Within the cohort, 4% (n=4) satisfied all 5 suggestive criteria. Five percent (n=5) satisfied 4 suggestive criteria, 6% (n=6) met at least 3 criteria, 4% (n=4) satisfied at least 2 criteria, 16% (n=16) at least one criteria and 65% (n=65) of the cohort did not meet any of the suggestive criteria. Figure 4.4 illustrates these findings.
Figure 4.3 Number of essential criteria satisfied by the cohort

Figure 4.4 Number of suggestive criteria satisfied by the cohort
4.5.2 Retrospective application of the ACOG objective criteria

Data were analysed further to determine whether the objective criteria are reflected in cases documented to have a perinatal aetiology at term. This was done by limiting the analysis to a well-defined group of cases in the cohort who have been identified by experts as having experienced intrapartum injury. Data on each of the 15 perinatal cases were retrospectively examined to determine the presence of each of the objective criteria. The findings are outlined below in table 4.26.

Table 4.26: Presence of objective criteria in term children with perinatal acquired cerebral palsy

<table>
<thead>
<tr>
<th>Cases</th>
<th>Ess-1</th>
<th>Ess-2</th>
<th>Ess-3</th>
<th>Ess-4</th>
<th>Sugg-1</th>
<th>Sugg-2</th>
<th>Sugg-3</th>
<th>Sugg-4</th>
<th>Sugg-5</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>√</td>
<td></td>
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Of the 15 cases documented to have a perinatal aetiology 40% (n=6) satisfied all 4 ACOG essential criteria for acute intrapartum hypoxia. Forty-seven percent (n=7) of cases met 3 criteria and 13% (n=2) satisfied 2 criteria. Among the 15 cases, 67% (n=10) had a recorded metabolic acidosis. All 15 cases had experienced an onset of neonatal encephalopathy within 24 hours. Sixty-seven percent (n=10) satisfied essential criteria 3. Within those 10 cases 40% (n=6) had a spastic quadriplegia and 27% (n=4) a dyskinesia. Ninety-three per cent (n=14) of cases satisfied essential criteria 4 in that they had other pathologies associated with CP excluded. Of the 15 cases considered to have a perinatal aetiology 60% (n=9) failed to satisfy all 4 ACOG essential criteria for acute intrapartum hypoxia.

Within the 15 cases in the perinatal aetiology group, 27% (n=4) satisfied all 5 suggestive criteria. Thirty-three percent (n=5) satisfied 4 suggestive criteria, 33% (n=5) satisfied 3 criteria and 7% (n=1) satisfied 2 criteria. The presence of a sentinel hypoxic event (suggestive criteria 1) occurred in 9 (60%) of the 15 cases. Fourteen (93%) of the 15 satisfied the fetal heart rate requirements of suggestive criteria 2. Suggestive criteria 3 (Apgar 0-3 beyond 5 minutes) was found in only 4 (27%) of the 15 cases. All 15 cases (100%) demonstrated multisystem failure within 72 hours of birth (suggestive criteria 4) and evidence of non-focal cerebral abnormality on early imaging (suggestive criteria 5). The number of term perinatal cases meeting each of the 9 ACOG criteria are outlined below in table 4.27.
Table 4.27: Number of term perinatal cases meeting each of the 9 ACOG criteria

<table>
<thead>
<tr>
<th>Essential Criteria</th>
<th>Number satisfied (%)</th>
<th>n=15</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 pH &lt; 7.00 and base deficit ≥ 12 mmol/L</td>
<td>10 (66)</td>
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<tr>
<td>2 Onset of neonatal encephalopathy within 24 hours</td>
<td>15 (100)</td>
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<tr>
<td>3 CP of the spastic quadriplegic or dyskinetic type</td>
<td>10 (66)</td>
<td></td>
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<tr>
<td>4 Exclusion of other pathologies associated with CP</td>
<td>14 (93)</td>
<td></td>
</tr>
<tr>
<td><strong>Suggestive but non-specific to asphyxia insults</strong></td>
<td></td>
<td></td>
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<tr>
<td>1 Sentinel hypoxic event</td>
<td>9 (60)</td>
<td></td>
</tr>
<tr>
<td>2 Sudden sustained fetal bradycardia or other evidence of non-reassuring fetal status</td>
<td>14 (93)</td>
<td></td>
</tr>
<tr>
<td>3 Apgar scores of 0-3 beyond 5 minutes</td>
<td>4 (27)</td>
<td></td>
</tr>
<tr>
<td>4 Multisystem failure within 72 hours of birth</td>
<td>15 (100)</td>
<td></td>
</tr>
<tr>
<td>5 Evidence of acute non-focal cerebral abnormality on early imaging</td>
<td>15 (100)</td>
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The authors of the objective criteria advocate that there are 4 essential criteria that identify severe hypoxia at birth and 5 suggestive criteria that if present together suggest intrapartum timing. At least 3 of the suggestive criteria have to be present to suggest an acute rather than chronic event. Examination of the 6 cases who meet all four essential criteria (Table 4.21), and so are identified as having severe hypoxia, shows that cases 7 and 14 meet all 5 suggestive criteria for an acute rather than chronic event, cases 3, 4 and 11 meet 4 of the suggestive criteria and case 15 meets 3 of the suggestive criteria. Therefore, all 6 of these cases meet the complete ACOG criteria for the identification of acute intrapartum hypoxia.

Further analysis of the cohort was undertaken to determine the distribution of cases meeting each essential criterion across the perinatal aetiology group as opposed to the other aetiology groups. As can be seen below in table 4.28, this analysis revealed that each of the 4 essential criteria was much more likely to occur in the perinatal aetiology subgroup than in the other aetiology groups.

<table>
<thead>
<tr>
<th>Essential Criteria</th>
<th>Perinatal group (n=15)</th>
<th>Other group (n=85)</th>
<th>RR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Metabolic acidosis</td>
<td>10</td>
<td>7</td>
<td>8.10 [3.66-17.92]</td>
</tr>
<tr>
<td>2 Neonatal encephalopathy</td>
<td>15</td>
<td>2</td>
<td>33.33 [8.79-113.40]</td>
</tr>
<tr>
<td>3 Spastic quadriplegia or dyskinesia</td>
<td>11</td>
<td>20</td>
<td>3.12 [1.91-5.09]</td>
</tr>
<tr>
<td>4 Exclusion of other pathologies</td>
<td>14</td>
<td>2</td>
<td>39.67 [10.02-157.07]</td>
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</table>

4.6 Conclusion

This chapter has provided a descriptive summary of the findings of the analysis of the study data. The principal findings of the data analysis will be discussed in chapter 5.
Chapter 5
Discussion of findings

5.1 Introduction

This chapter discusses the principal findings of the data analysis in chapter 4 in the context of current literature. This cohort study sought to apply objective criteria for the identification of acute intrapartum hypoxia to a cohort of children with cerebral palsy and to describe other cerebral palsy related factors in the cohort. Data in the form of antepartum, intrapartum, newborn, neonatal and paediatric variables were explored. Overall, the results of the analysis performed on the study data offer a comprehensive picture of cerebral palsy in the West of Ireland and support those from previous research in other jurisdictions.

This chapter will begin by outlining the prevalence of cerebral palsy in the West of Ireland. The chapter then goes on to discuss the findings of the data analysis in describing the antepartum, intrapartum, newborn, neonatal and paediatric variables related to cerebral palsy in the cohort. The chapter will then discuss the retrospective application of the ACOG criteria for the identification of acute intrapartum hypoxia to the cohort.

5.2 Prevalence of Cerebral Palsy

Measures of prevalence were undertaken to determine the frequency of occurrence of cerebral palsy in the West of Ireland for the birth years 1990-2000. This cohort study found a prevalence rate for the years 1990-2000 of 1.9/1,000 live births (95% Confidence Intervals [CI] 1.6-2.2). This does not differ substantially from that reported in other studies. Johnson (2002) reports a European prevalence rate of 2.08/ 1,000 live births (95% CI 2.02-2.4). A prevalence rate of 2.07/ 1,000 live births (95% CI 2.01-2.3) was reported for Northern Ireland by Parkes et al (2005). Sigurdardottir et al (2009) report a prevalence of 2.2/ 1,000 live births (95% CI 1.8-2.8) for Iceland. Prevalence rates in other geographical areas in Ireland are also similar. The South of Ireland cerebral palsy registers reports a prevalence rate of 1.91/1,000 live births (95% CI 1.60-2.27) and the East of Ireland reports a rate of 1.92/1,000 live births (95% CI 1.72-2.14) (European Perinatal Health Report, 2008).

Previous studies have reported prevalence rates of cerebral palsy varying between 1.5 and 3.0 per 1,000 live births (Dear & Newell, 2001; Clarke & Hankins, 2003). Differences in prevalence rates found among studies may be a result of inconsistencies in the way in which cerebral palsy is defined and its subtypes classified. Variations in the manner in which cases are ascertained also affect the calculation of prevalence rates. Cases are ascertained from multiple sources including community and hospital-based paediatricians, physiotherapists, health centres, general practitioners, child development organisations and population based registers. This study had to depend on case ascertainment previously conducted by the WICPR and the service providers interacting with children with cerebral palsy in the West of Ireland. The study proceeded on the assumption that there are 156 children in the West of Ireland born between 1990-2000 with cerebral palsy but it is possible that there are more whom the service providers have not identified.
However, those involved in setting up the register (WICPR) are confident that they achieved full case ascertainment (Mongan, 2006). Whether or not post-neonatal cerebral palsy and children with cerebral palsy who have died are included in registers also affects the calculation of prevalence rates. The need for consent before including children with cerebral palsy on registers may also affect the calculation of prevalence. It is imperative that a uniform standard is applied across all recording of information about cerebral palsy so that data can be compared appropriately and aggregated appropriately to facilitate ongoing research into the condition. The use of the SCPE definition and classifications by the European registers should minimise this problem as it provides uniformity and consistency.

A lot of what we know about cerebral palsy comes from studies originating in population-based registers (SCPE, 2000; Mongan et al, 2006; Surman et al, 2006). Such population-based registers are invaluable in the provision of epidemiological data of sufficient size to make meaningful comparisons with other registers and geographical areas (Bax et al, 2005: Blair & Love, 2005). There are two other cerebral palsy registers in the Republic of Ireland. It would be very beneficial for cerebral palsy surveillance and research if a single, complete Republic of Ireland cerebral palsy register combining data held on the Eastern, Southern and Western registers were created. This would provide a single source with a critical mass of comprehensive information about rates, causes and consequences of cerebral palsy and act as a valuable research resource. Ireland, because of its small size, is well suited to a single national register. There are a limited number of facilities providing care to children with cerebral palsy so it should not be too difficult to have a well established network of relatively few professionals so that case ascertainment and agreement on diagnosis is not problematic. A single national register would also ensure consistent terminology for the definitions and classification of cerebral palsy and its subtypes. This study could then be replicated on an all-Ireland basis. The methods chosen for this study could easily be reproduced at a later date using the same format on a national scale. This would provide a comprehensive national picture of cerebral palsy in Ireland.

The data contained on a national register could provide an accurate assessment of cerebral palsy trends over time, information about the impact of changes in care on the prevalence of cerebral palsy and could facilitate the exploration of aetiological questions or unusual clusters of events. The findings could also inform decisions about resource allocation and social policy and health policy decisions, particularly around future population needs. The type of data available on a national register would enable auditing and benchmarking by facilitating the systematic surveillance of both short and long-term clinical outcomes, which is critical for effective clinical governance. Linking the National cerebral palsy register to the country’s death notification system would help generate data about survival rates, life expectancies and the relationship of survival to the severity of the condition and its associated impairments. Long term follow-up of children enrolled in large, population-based studies are needed to continue research efforts into explaining and preventing cerebral palsy. Population-based registers are instrumental in such studies and a national register would contribute greatly to such research. The availability of a substantial number of cases on a national register would enable researchers to separate the sample into more homogeneous
subgroups to enable research on risk factors, aetiology and causal pathways in specific groups thereby enhancing our understanding of this complex condition.

5.3 Description of the Cerebral Palsy related factors in the cohort

Evidence from epidemiological studies has identified a range of major pathologies associated with cerebral palsy and the description of the sample provided in chapter 4 includes information about those associated pathologies. Antenatal, intrapartum and neonatal factors associated with cerebral palsy reported in this study were identified from the literature. The majority of studies in the literature were case-control studies. No single risk factor has been consistently associated with cerebral palsy across all studies. This is due to the variety of study designs, outcomes examined, weight groups studied, gestation groups studied and the various definitions of the variables included in the studies. However, the following major pathologies associated with cerebral palsy (Table 5.1) have been identified in the literature and so are explored in the following discussion on a range of demographic and clinical characteristics in both the maternal and neonatal sample.

Table 5.1 Major Pathologies associated with Cerebral Palsy

<table>
<thead>
<tr>
<th>Antenatal Factors</th>
<th>Intrapartum Factors</th>
<th>Neonatal Factors</th>
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<tr>
<td>Maternal illness</td>
<td>Pyrexia in labour</td>
<td>Birth weight</td>
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<tr>
<td>Maternal infection</td>
<td>Mode of birth</td>
<td>Prematurity</td>
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<tr>
<td>Coagulopathies</td>
<td>Acute intrapartum event</td>
<td>Apgar score</td>
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<tr>
<td>Antepartum haemorrhage</td>
<td>Non-reassuring fetal status</td>
<td>Acid-base status</td>
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<tr>
<td>Congenital abnormalities</td>
<td>Placental pathology</td>
<td>NICU admission</td>
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<tr>
<td>Gestation</td>
<td>Cord incident</td>
<td>Neonatal illness</td>
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<tr>
<td>Multiple birth</td>
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<td>Encephalopathy</td>
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<tr>
<td>Growth restriction</td>
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<td>Cerebral imaging</td>
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<td>Genetic</td>
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5.3.1 Description of the maternal sample

The mother's age at delivery ranged from 16 to 44 years with a mean of 30 years. The average age of all mothers in Ireland in 1990 was 29 years, and in 1999 was 30 years (ESRI, 2002). A Swedish case-control study by Thornberg-Jerneck & Herbst (2006) found that women younger than 20 years and older than 35 years were more likely to have a baby with cerebral palsy. Similarly, Wu et al (2006) found that mothers over 35 years were more likely to have a baby with cerebral palsy than those less than 35 years. Four (4%) of the mothers in this cohort were under 20 years and 26 (26%) were over 35 years, with 7 of the mothers being over 40 years old. Badawi et al (1998) found that the risk of newborn encephalopathy, a known risk factor for cerebral palsy, increased significantly with increasing maternal age, particularly in mothers over 35 years. In contrast, there was only 1 case of mild encephalopathy and 2 cases of severe encephalopathy in the babies born to mothers over the age of 35 years in this study. The remaining 16 cases of encephalopathy were found in babies born to mothers younger than 35 years.

In this study 41 (41%) women were first time mothers and 59 (59%) had previous children. Thornberg-Jerneck & Herbst (2006) concluded that cerebral palsy was more frequent in the first child especially if that first child was born to mothers older than 34 years. Only 3 (3%) of the
mothers in this study were over 34 years old and first time mothers. In contrast, case-control studies by Murphy et al (1995) and Gray et al (2001) both conclude that parity greater than 3 increased the risk of cerebral palsy. In this study cohort 16 (16%) of the women were having their 4th or subsequent child. Mahony et al (2009) conducted a retrospective review (n=77,838) examining the influence of parity on cerebral palsy following neonatal encephalopathy and seizures in term singleton infants. They concluded that neonatal encephalopathy with seizures occurred more frequently in primiparous women than multiparous women. Primiparous women were more likely to have experienced intrapartum hypoxia in association with the neonatal encephalopathy and have a higher incidence of cerebral palsy following encephalopathy than multiparous women. In this study 37% of the neonatal encephalopathy cases (n=7) occurred in primiparous women and 63% (n=12) in multiparous women.

It is, however, very difficult to unravel the individual effects of maternal age and parity as they are strongly correlated. Recent data from the Economic and Social Research Institute (ESRI, 2002, 2011) in Ireland shows that 27.6% of mothers giving birth in 2009 were aged 35 years or older, up from 22% in 2000 and 20% in 1990. The proportion of mothers giving birth for the first time at age 35 or more increased from 13.7% in 2005 to 14.9% in 2009. With the average age of mothers increasing and the proportions of older first time mothers increasing, it is likely that these two factors will become more significant risk factors for cerebral palsy into the future. As we now have European wide data on the SCPE register concerning thousands of cerebral palsy children born since 1976, further epidemiological studies are possible to establish the contribution of age and parity as risk factors associated with cerebral palsy and the changing profile of those particular risk factors over the decades.

Epidemiological studies have identified a number of maternal illnesses associated with cerebral palsy including; hypothyroidism, seizures, diabetes, renal disease, cardiac disease, coagulopathies and hypertension. One third of women in this study had a documented antenatal illness that may have been associated with the baby's cerebral palsy diagnosis. Along with certain maternal illnesses, antenatal infection and, in particular chorioamnionitis has been associated with an increased risk of cerebral palsy in numerous studies (Yoon et al, 2003; Wu et al, 2003; Neufield et al, 2005; Mann et al, 2009). This is particularly true for the premature infant who is especially vulnerable to both infection and cerebral damage. In this study prematurity (RR 1.97 [CI 1.20-3.22]) was more frequent in the women with antenatal infection/chorioamnionitis than those without signs of infection. Five (5%) of the mothers in this study had a confirmed antenatal infection. In addition to the mothers experiencing antenatal infection, 5 (5%) more mothers had a prolonged rupture of membranes. Antenatal infection, chorioamnionitis and prolonged rupture of membranes are often associated with pyrexia in labour but in this cohort, none of the 10 women with signs of intrauterine infection had intrapartum pyrexia documented in their records. Three of the 10 (30%) mothers had indications of inflammation on placental pathology, in 1 case associated with antenatal infection and in 2 other cases associated with prolonged rupture of membranes. Antenatal infection, chorioamnionitis and prolonged rupture of membranes are associated with prematurity and that was found to be the case in this study. Seven of the 10 women (70%) with signs of intrauterine
infection (antenatal infection and/or PROM) subsequently gave birth to a premature baby. Abundant clinical evidence indicates that intrauterine exposure to maternal infection or inflammation is associated with increased mortality and morbidity in the baby (Murphy et al, 1995; Wu & Colford, 2000; Yoon et al, 2003; Wu et al, 2003; Neufield et al, 2005; Mann et al, 2009). In this study the occurrence of metabolic acidosis (RR 1.20 [95%CI 0.32-4.51]), Apgar scores <6 @ 5 minutes (RR 1.38 [95%CI 0.36-5.28]) and abnormal CTG (RR 1.50 [95%CI 0.85-2.64]) were slightly increased in the antenatal infection/chorioamnionitis group compared to women without signs of infection.

There are a number of factors during labour and birth that have been found to be associated with cerebral palsy. Among those factors are the mode of birth, fetal position, shoulder dystocia, meconium stained liquor, antepartum haemorrhage, maternal pyrexia in labour and pathological CTG. These intrapartum factors were explored in this study.

A number of studies have found associations between mode of birth and cerebral palsy. Jacobsson et al (2002) found a significant association between instrumental births and cerebral palsy and between emergency caesarean section and cerebral palsy. Similarly high rates of instrumental vaginal and caesarean section births were found in this study. Seventeen (17%) babies in this study were born by instrumental birth and 28 (28%) were by caesarean section including 23 (82%) of which were emergency caesarean sections. The ESRI (2002) report national caesarean section rates of 11% for 1990 and 21% for 1999, yet 28% of children in this cerebral palsy cohort were delivered by caesarean section. Similarly, ESRI (2002) report national instrumental delivery rates of 12% for 1990 and 15% for 1999, yet 17% of children in this cerebral palsy cohort were born by instrumental birth.

Analysis of neonatal outcomes showed that the occurrence of neonatal encephalopathy (RR 2.85 [95%CI 1.32-6.17]), metabolic acidosis (RR 1.50 [95%CI 0.56-4.05]), Apgar scores <6 @ 5 minutes (RR 1.2 [95%CI 0.39-3.86]) and abnormal CTG (RR 1.63 [95%CI 1.00-2.66]) were more frequent in the instrumental births group. Admission to the neonatal unit (RR 0.81 [95%CI 0.51-1.31]) was not.

Analysis of neonatal outcomes showed that the occurrence of metabolic acidosis (RR 1.83 [95%CI 0.76-4.40]), Apgar scores <6 @ 5 minutes (RR 1.22 [95%CI 0.43-3.46]) abnormal CTG (RR 3.35 [95%CI 2.22-5.04]) and admission to the neonatal unit (RR 1.46 [95%CI 1.14-1.85]) were more frequent in the emergency caesarean section group.

A number of studies have found associations between mode of birth and encephalopathy. The presence of neonatal encephalopathy has been identified as the strongest neonatal predictor of cerebral palsy (Nelson, 2002; Dixon et al, 2002). Badawi et al (1998b) found a significant association between instrumental births and encephalopathy, and between emergency caesarean section and encephalopathy. Analysis of this study cohort did not find an association between neonatal encephalopathy (RR 0.89 [95%CI 0.33-2.43]) and emergency caesarean section but did find an association with instrumental births (RR 2.85 [95%CI 1.32-6.17]).
Internationally, breech births account for a relatively small proportion of births, approximately 4% (European Perinatal Health Report, 2008) but accounted for a large 14% of the births in this cohort of cerebral palsy children. Breech delivery is associated with increased perinatal morbidity and mortality (Anderson et al, 2009; Hannah et al, 2000; Hofmeyr & Hannah, 2003) but evidence for an association between breech birth and cerebral palsy is contradictory. Jacobsson et al (2002) found a significant association between breech births and cerebral palsy. Andersen et al (2009) also report a similar association and found singletons born vaginally at term to be particularly at risk compared with those delivered by caesarean section. In contrast, Ozturk et al (2007) did not find any association between breech birth and cerebral palsy. Approximately 25% of fetuses are in the breech position at 32 weeks gestation falling to about 3% at term. All of the breech babies in this study (n=14) were preterm. European wide, 80% or more breech babies are delivered by caesarean section (European Perinatal Health Report, 2008). This reflects the current belief that planned caesarean section reduces adverse perinatal outcome in the case of breech presentation. In this cohort 6 (43%) of the babies presenting breech were born by caesarean section with the remaining 8 (57%) born vaginally. This can be explained by the breech babies being premature and the 8 vaginally born babies all had precipitous births that did not allow time for caesarean section.

It is often speculated that birth asphyxia could be part of the causal pathway leading to cerebral palsy in association with breech birth (Andersen et al, 2009). Of note, 5 (36%) of the breech babies had an Apgar score below 6 at 1 minute and 2 (14%) had score below 6 persisting at 5 minutes. Three (21%) of the breech babies had a metabolic acidosis at birth. None of the breech babies subsequently developed encephalopathy and so it can be concluded that none had experienced a significant hypoxic ischaemic event. It is probable that the low Apgar scores were actually related to prematurity rather than birth asphyxia. Premature babies always have decreased muscle tone at birth and often have respiratory compromise so will score lower for these parameters on their Apgar score.

Although persistent occipito-posterior position and shoulder dystocia have been associated with cerebral palsy in some studies, they occurred very infrequently in this particular cohort (1 persistent occipito-posterior and 2 shoulder dystocia cases) making it difficult to draw conclusions about any associations with cerebral palsy.

Meconium stained liquor occurred in 17 cases (17%) in the cohort. Approximately 20% of all births are affected by meconium and the vast majority do not develop cerebral palsy (Nelson & Grether, 1998). The significance of meconium stained amniotic fluid and whether or not it reflects a non-reassuring fetal status remains uncertain (Ciftci et al, 1999; Ziadeh et al, 2000; ACOG, 2003; Ahanya et al, 2004). On further examination of the 17 babies with meconium stained amniotic fluid, 10 (59%) of them had an Apgar score below 6 at 1 minute and 7 (41%) had an Apgar below 6 at 5 minutes. The Apgar scores for these 17 babies with meconium stained amniotic fluid indicate that 10 of them were in less than optimal condition at birth and 7 remained so at 5 minutes after birth.
Sixteen (94%) of the babies were full term and so prematurity cannot account for the low Apgar scores. Four (23%) of the 17 had a metabolic acidosis documented and went on to subsequently have a moderate (1 case) or severe (3 cases) encephalopathy. Nine (53%) of the 17 cases experienced neonatal seizures and 8 (47%) experienced meconium aspiration syndrome in the neonatal period. So, although it is widely accepted that meconium staining is not a reliable indicator of intrapartum distress or potential adverse outcome, it was associated with an increased occurrence of neonatal encephalopathy (RR 4.39 [95%CI 2.11-9.15]), metabolic acidosis (RR 1.50 [95%CI 0.56-4.05]), Apgar scores <6 @ 5 minutes (RR 4.27 [95%CI 1.79-10.20]), abnormal CTG (RR 1.85 [95%CI 1.17-2.93]) and neonatal seizures (RR 5.49 [95%CI 2.48-12.18]) in this study.

Nathan et al (1994) report similar findings. They studied 42,000 term singleton newborns and found a higher incidence of low 1 and 5 minute Apgar scores, umbilical artery pH of 7 or less, and seizures in the neonatal period among newborns with meconium stained liquor.

Associations between placental abruption and cerebral palsy have been found in some studies (Jacobsson et al, 2002; Greenwood et al, 2005; Stelmach et al, 2005). Placental abruption refers to the detachment of part or the entire placenta from its implantation site before the birth of the baby and accounts for 35% of bleeding in later pregnancy (Henderson & MacDonald, 2004). It occurs in 1-2% of pregnancies and is associated with increased perinatal morbidity and mortality (Fraser & Cooper, 2004). There were 14 cases of placental abruption in this cohort. Hypertension and pre-eclampsia are risk factors for abruption and two of the mothers (14%) who experienced abruption had pregnancy induced hypertension and 3 (21%) had pre-eclampsia. Increased maternal age and parity are also risk factors for placental abruption but in this cohort eleven (78%) of the mothers were under 35 years old and so were not of increased maternal age. Two (14%) mothers were 37 years old, one (7%) was 39, and all three of those women had hypertension. This illustrates the often co-existing risk factors and the difficulties this creates when drawing inferences about strength of associations between risk factors and outcomes. Most of the mothers experiencing placental abruption (n=12, 86%) had a parity of 2 or under, one mother (7%) was a para 5 and the other (7%) was a para 9. The para 9 mother was 39 years old, had no antenatal care, had severe pre-eclampsia, a pathological CTG and a premature baby and so had multiple risk factors for adverse outcome and cerebral palsy.

Placental abruption often precedes premature birth (Fraser & Cooper, 2004). Ten of the 14 mothers (71%) with abruption in this study delivered premature babies giving a risk ratio of 2.12 ([95%CI 1.36-3.30]) for prematurity associated with placental abruption. Maternal shock from haemorrhage caused by abruption can compromise the fetus. In this study the occurrence of neonatal encephalopathy (RR 1.89 [95%CI 0.72-4.98]), metabolic acidosis (RR 5.46 [95%CI 2.54-11.76]), Apgar scores <6 @ 5 minutes (RR 1.54 [95%CI 0.50-4.76]), abnormal CTG (RR 1.78 [95%CI 1.10-2.98]), and admission to neonatal unit (RR 1.70 [95%CI 1.38-2.09]) were all more frequent in the placental abruption group than those without that risk factor. Of the 14 cases of abruption, 6 (43%) had a pathological CTG, 3 (21%) had a suspicious CTG, 5 (36%) had 1-minute Apgar scores below 6 and 3 (21%) had 5-minute Apgars below 6. Eight (57%) of the 14 babies had a metabolic acidosis at birth and 4 (28%) went on to develop severe encephalopathy. It is known
that abruption is associated with cerebral palsy. However, it is also known that increasing maternal age and parity, hypertension and non-reassuring fetal status are associated with cerebral palsy but these are also associated with abruption. This information illustrates very clearly the all too common problem of confounding variables in cerebral palsy studies and makes it difficult to draw any firm conclusions about abruption as a standalone risk factor for cerebral palsy.

A number of studies have observed that pyrexia in labour is an antecedent of cerebral damage, low Apgar scores and encephalopathy and is associated with cerebral palsy (Badawi et al, 1998b; Wu & Colford, 2000; Impey et al, 2001; Graham et al, 2004; Greenwood et al, 2005; Nelson, 2009). Similarly, this study found that the occurrence of neonatal encephalopathy (RR 1.87 [95%CI 0.63-5.54]), metabolic acidosis (RR 1.73 [95%CI 0.59-5.10]) and Apgar scores <6 @ 5 minutes (RR 1.24 [95%CI 0.32-4.80]), were all more frequent in the maternal pyrexia in labour group than in women without pyrexia in labour. Eleven (11%) of the mothers in the cohort had a pyrexia in labour; four (36%) of whom had a documented antenatal infection and 2 (18%) of whom had a preterm baby. Pyrexia, when it is a proxy for inflammation and infection, may increase the vulnerability of the fetal brain to damage and may also have a role in initiating preterm birth (Wu & Colford, 2000), both of which are associated with cerebral palsy. Five (45%) of the 11 babies born to mothers with an intrapartum pyrexia were preterm and 6 (55%) were term. Three (60%) of those preterm babies had periventricular leukomalacia (PVL) on cerebral imaging and 2 (33%) of the 6 term babies had cerebral ischaemia and infarcts on their cerebral imaging indicating antenatal cerebral damage. Two (33%) of the 6 term babies born following pyrexia in labour had a metabolic acidosis at birth and three (50%) went on to develop severe encephalopathy. Seven of the 11 (64%) placentas were examined for pathology and 2 (18%) were found to have inflammation consistent with chorioamnionitis. Unfortunately, there were no records in any of the 11 maternal charts of high vaginal swabs being taken or analysed and so it is difficult to draw any firm conclusions about the rates of maternal intrapartum infection in this cohort.

The difficulty with studying the association between pyrexia in labour and cerebral palsy is that maternal pyrexia is a poor proxy for maternal infection. Without additional clinical and histological information, it is unreasonable to conclude that maternal pyrexia always indicates infection. Maternal pyrexia is also associated with epidural analgesia, induction of labour, prolonged labour, instrumental birth and nulliparity (Nelson & Willoughby, 2000; Wu & Colford, 2000; Impey et al, 2001). Among the 11 mothers with intrapartum pyrexia in this study, there were a number of factors other than infection that may have contributed to the pyrexia. Nine (82%) of the mothers were primigravid, 3 (27%) were induced and 5 (45%) had instrumental births. All of these factors have been found in studies to be associated with maternal pyrexia in labour.

Abnormal fetal heart rate patterns may reflect intrauterine fetal hypoxia (Nelson et al, 1996). However, abnormal fetal heart rate patterns observed during labour may also reflect pre-existing neurological injury of the fetus, fetal anomaly, the effects of medications, fetal injury and infection (Nelson et al, 1996; Pateman et al, 2008). The correlation of fetal heart rate patterns with outcome is problematic because abnormal fetal heart rate patterns have a high false-positive rate as a
predictor of fetal hypoxia and neonatal outcome (Nelson et al, 1996; Fahey & King, 2005). Most mothers with non-reassuring fetal heart rate patterns go on to give birth to babies with normal Apgar scores (Nelson et al, 1996). Studies have suggested that in the presence of intrauterine fetal hypoxia, the abnormal CTG is usually accompanied by metabolic acidosis in the fetus or newborn, low Apgar score and neonatal encephalopathy (Larma et al, 2007). Similarly, this study found that those with abnormal CTG had an increased occurrence of neonatal encephalopathy (RR 7.24 [95%CI 2.25-23.25]), metabolic acidosis (RR 5.88 [95%CI 1.79-19.34]), and Apgar scores <6 @ 5 minutes (RR 3.73 [95%CI 1.28-10.91]). The abnormal CTG group were also more likely to experience abruption (RR 3.05 [95%CI 1.01-9.25]), meconium stained liquor (RR 2.49 [95%CI 1.00-6.19]) and operative delivery (RR 4.07 [95%CI 2.25-7.38]).

Despite the failings of fetal heart rate monitoring in reducing intrapartum mortality it has become an integral part of modern intrapartum care. Ninety eight (98%) women in this study underwent electronic fetal monitoring in the form of a CTG. Studies have shown that substandard care around interpretation of and response to fetal heart rate patterns have contributed to intrapartum mortality and morbidity (Gaffney et al, 1994; CMACE, 2011) Closed claims review of clinical negligence litigation cases have also found significant incidences of incorrect interpretation and slow response to abnormal fetal heart rate patterns in labour (Ennis & Vincent, 1990; Vincent et al,1991; Williams & Arulkumaran, 2004). In recognition of its poor predictive value, supplementary tests such as fetal blood gases, lactate levels or electrocardiography are recommended to confirm the diagnosis of hypoxia before operative interventions take place. Interventions for risk reduction around the use of fetal heart rate monitoring in labour include compulsory training in CTG interpretation, practice guidelines around appropriate and timely intervention and proper documentation by the entire maternity care team (Miller, 2011b). Currently, expert system decision support software for the assessment of CTG is being tested in a multicentre randomised control trial (INFANT, 2010). These measures may go some way towards mitigating the prominent role of the CTG in clinical litigation cases. A significant proportion (30%) of the women in this study had a pathological CTG, with 10% experiencing a suspicious CTG. It is imperative that maternity care providers are equipped to act on these abnormal fetal heart rate patterns when they occur.

In summary, mothers in this cohort are similar to other cohorts in terms of demographics. Mothers in this cohort experienced similar antenatal and intrapartum factors associated with cerebral palsy as those identified in other cohorts in the literature.

5.3.2 Description of the neonatal sample

The gestational age at delivery of children in this cohort ranged from 24 to 42 weeks with a median of 39 weeks. The majority (61%, n=61) of children with cerebral palsy were born at term. This is consistent with most other studies. Although term babies are at relatively low absolute risk of cerebral palsy, they constitute the large majority of all births. Preterm birth is a recognised risk factor for cerebral palsy and the risk increases as the gestational age decreases. Thirty-nine (39%) of the children in this study were born prematurely. Cerebral palsy is also associated strongly with birth weight with the risk increasing with declining birth weight. Low birth weight babies (<2500
grams) accounted for 40% of the babies in this study. Gestational age and birth weight are important determinants of cerebral palsy rates. Among all live births in Ireland in 1990, 3.6% were of low birth weight increasing to 4.3% in 2000 and 5.3% in 2009 (ESRI, 2002, 2011). Prematurity affected 4.2% of live births in Ireland in 1990 increasing to 5.3% in 2000 and 6% in 2009 (ESRI, 2002, 2011). These continually rising rates of prematurity and low birth weight have significant implications for the epidemiology of cerebral palsy.

The distribution of cerebral palsy cases by gestational age and birth weight in this study was similar to that found in other jurisdictions. Table 5.2 illustrates comparative data on the birth weight and gestational age distribution among cerebral palsy cohorts in 4 different jurisdictions. Variations in the proportions of the most immature (<28 weeks) and the smallest (<1000 grams) babies in different jurisdictions probably reflect local policies around resuscitation and management of the extremely premature in those birth years.

Table 5.2: Cerebral palsy distribution by gestational age and weight across 4 databases

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<td>&lt; 28 weeks</td>
<td>11%</td>
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<td>28-32 weeks</td>
<td>18%</td>
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<td>33-37 weeks</td>
<td>10%</td>
<td>8%</td>
<td>19%</td>
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<td>&gt;37 weeks</td>
<td>61%</td>
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<td>Birth Weight</td>
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<tr>
<td>&lt; 1,000 grams</td>
<td>11%</td>
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<td>5%</td>
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<td>1,000-1499 grams</td>
<td>12%</td>
<td>11%</td>
<td>15%</td>
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<td>1,500-2499 grams</td>
<td>17%</td>
<td>26%</td>
<td>24%</td>
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<tr>
<td>&gt;2500 grams</td>
<td>60%</td>
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Multiple births are risk factor for cerebral palsy. European data indicates that children born from multiple pregnancies are at more than 4 times greater risk for cerebral palsy than singletons (RR 4.36 [95%CI 3.76-4.97]) (Topp et al, 2004). The increased risk of cerebral palsy with multiple births is chiefly related to the higher rate of prematurity and intra-uterine death of a co-twin or triplet (Topp et al, 2004; Pharoah & Dundar, 2009). Multiple births accounted for 11% (n=11) of the cohort in this Irish study. The gestational age of the multiples ranged from 27 to 35 weeks and 91% (n=10) were born before 32 weeks. This is to be expected as multiple birth babies are more likely to be born prematurely. Parkes et al (2005) report a multiple rate of 10% in their Northern Ireland cerebral palsy cohort and Sigurdardottir et al (2009) report that 13% of the cerebral palsy children born in Iceland between 1990 and 1996 were from multiple births. The European data collated by SCPE (2002) reports a rate of 14%. The rate of multiple births in Ireland continues to rise, with a rate of 2% in 1990, 2.6% in 2000 and 3.1% being reported by the ESRI for 2009 (ESRI, 2002, 2011). The rising rate of multiples is largely attributed to increasing maternal age and the use of fertility treatment (European Perinatal Health Report, 2008; Wayman, 2011). As the risk of cerebral palsy is higher in multiples than in singletons, increasing rates of multiple births in Ireland and across Europe has implications for the epidemiology of cerebral palsy.
Multiple births are a potential area to target for the prevention of cerebral palsy. The recently established HSE National Obstetrics and Gynaecology Clinical Care Programme target the reduction of multiple births after fertility treatment as one of its objectives (www.hse.ie). The European Union Foundation for the Care of Newborn Infants (EFCNI, 2011) addresses the question of prematurity due to multiple births in its EU benchmarking Report (2009-2010). They recognise the need to reduce the prevalence of preterm birth together with its associated morbidity and mortality. Efforts must continue to address delayed childbearing and the transfer of multiple embryos with fertility treatment. These are the two most significant factors contributing to increasing rates of multiple births. Monochorionic twins are at greater risk than dichorionic because of their shared circulation and so these babies must be a particular focus for research attention (Minakami, 1999). As a significant risk factor for cerebral palsy, multiple births should continue to be the subject of close surveillance in an effort to reduce the associated mortality and morbidity.

The male: female ratio found in this study was 1.7:1 giving a relative risk (RR) of cerebral palsy among males of 1.7 [95%CI 1.27-2.29]. The finding of an increased risk of cerebral palsy in males is in keeping with findings from other studies. The European data collated by SCPE (2002) reports a male: female ratio of 1.33:1 and found that all 14 centres reported more males than females. The Northern Ireland Cerebral palsy Register reports a ratio of 1.2:1 (Parkes et al, 2005) and studies by Thorngren-Jerneck & Herbst (2006) report a Swedish ratio of 1.55:1. Evidence suggests that the male embryo is more vulnerable than the female with the male fetus at greater risk of death or damage (Hanson et al, 1999; Kraemer, 2000; Smith, 2000). Perinatal brain damage, cerebral palsy, congenital deformities, premature birth and stillbirth are commoner in male babies (Mizuno, 2000). Male babies have a higher risk of adverse outcomes in the neonatal period and this vulnerability continues to exist throughout their lives (Glezerman, 2009). ESRI (2002) data reports a perinatal mortality rate of 8.1/1000 among males and 7.2/1000 among females. Male babies are relatively more vulnerable than female babies are to growth restriction (Spinillo et al, 1994; Jarvis et al, 2005). Growth restriction is a risk factor for cerebral palsy and so will increase the vulnerability of male babies. Male babies are also physiologically less mature than females. This is specifically true for cerebral anatomy and so makes the male brain more vulnerable to insult (Jarvis et al, 2006). These inherent male vulnerabilities may account for the greater proportion of males with cerebral palsy than females.

The risk of cerebral palsy increases with persistent low Apgar Scores. A low Apgar score alone is a poor predictor of long-term neurologic outcome. However, some studies have demonstrated a good correlation between persistent low Apgar score and neurological disability (ACOG, 2003). Defining the numerical value that represents a low Apgar of significance is still the subject of debate. Murphy et al (1997) found that an Apgar score <3 at 5 minutes was associated with an increased risk of cerebral palsy, while Thorngren-Jerneck & Herbst (2001) found that a 5 minute score < 7 was associated with an increased risk. In this current study cohort, an Apgar score of ≤ 6 was recorded in 35% (n=35) of the cohort at 1-minute and in 15% (n=15) of the cohort at 5-minutes. A further study by Thorngren-Jerneck & Herbst in 2006 found that the highest risk for cerebral palsy was associated with a 1-minute score of 1 and a 5-minute score of 3. The ACOG has taken a
position that an Apgar score 0-3 after 5 minutes is an appropriate criterion for use as a potential marker of intrapartum asphyxia. An Apgar score of ≤3 was recorded in 12% (n=12) of the cohort in this study at 1-minute and in 5% (n=5) of the cohort at 5-minutes. The occurrence of abnormal CTG, metabolic acidosis, seizures and neonatal encephalopathy in this study were all more frequent in babies with an Apgar scores <6 @ 5 minutes and with Apgar scores <3 @ 5 minutes. Only 35% (n=35) of the cohort had 10-minute Apgar scores recorded. Of the available 10 minute Apgar scores (n=35), only 4 children (12%) recorded an Apgar score of < 6 with no child having a score <3.

The absence of 10-minute Apgar scores in the records is worthy of remark in cases where the 5 minute score is concerning. In clinical practice, if the 5-minute Apgar score is indicating that the condition of the baby is satisfactory, then 10-minute scoring is not warranted. However, if the 5-minute score is indicating that the baby remains compromised, the 10-minute score is necessary not only to provide information about the ongoing condition of the baby but also to provide vital information about the effectiveness of the baby’s resuscitation by care providers. It is important that care providers carefully record Apgar scores. They are often the only indication available in records of the baby’s overall condition at birth and in the time immediately following birth. The decision to initiate resuscitation measures is based partly on the Apgar score, which in turn is based on the baby’s condition, and so should be recorded diligently and accurately. Each of the 5 parameters making up the Apgar score (heart rate, respirations, muscle tone, reflex irritability and colour) should be recorded separately before applying an overall score. While collecting data for this study from the records it was often the case that overall scores were recorded but no breakdown of the various parameters of the score were available. There were also a number of cases where the Apgar scores recorded were not congruent with the descriptions of the level of resuscitation provided to the baby. In one case, Apgars were recorded as ‘9 @ 1, 10 @ 5’ which indicates a baby in good condition, but the care provider then documented 3 minutes of bag and mask ventilation for a baby described as ‘flat at birth’. Of greater concern were 2 cases where it was obvious that Apgar scores had been subsequently altered by someone but the alteration was not signed, dated or explained. The application of Apgar scores is further complicated by inter-observer inconsistencies (Moster et al, 2001; Kveim et al, 2010). Regardless of the poor value of the Apgar score as an indicator for intrapartum compromise or a predictor of adverse neurological outcome, it is the tool used universally to describe the condition of babies at birth and so should be recorded with due diligence in medical records. As more and more of these babies become the subject of litigation, poor documentation is causing increasing difficulties for care providers when they are attempting to defend their practice.

As expected, those children with persisting low Apgar scores underwent the most intense resuscitation. Chest compressions and resuscitation drugs are the two most intense levels of resuscitation used in clinical practice and are reserved for very seriously compromised babies. Only 4 (4%) babies required chest compressions. Of the 4 babies requiring compressions, two also received resuscitation drugs. These 4 babies in the sample all had intrapartum hypoxia, metabolic
acidosis, required intubation and went on to have neonatal encephalopathy and so were seriously compromised babies.

Although it is the case that most infants with evidence of intrapartum asphyxia do not develop serious long-term sequelae, the risk of poor neonatal outcomes increases in newborns with blood gas values that reflect a metabolic acidosis (Malin et al 2010). In this study the occurrence of neonatal encephalopathy (RR 6.97 [95%CI 3.09-15.72]), abnormal CTG (RR 3.34 [95%CI 2.08-5.37]), operative birth (RR 2.71 [95%CI 1.53-4.80]), Apgar scores <6 @ 5 minutes (RR 8.79 [95%CI 3.36-22.97]), acute intrapartum events (RR 3.49 [95%CI 2.32-5.25]) and admission to NICU (RR 2.07 [95%CI 1.63-2.63]) were all more frequent in babies with metabolic acidosis than those without. Intrapartum metabolic acidosis arises after significant intrapartum asphyxia. Evidence of metabolic acidosis is considered to be present if the pH <7.00 and the base deficit ≥ 12 mmol/L (Goodwin et al, 1992; MacLennan, 1999; Low, 2004). Seventeen babies (17%) in this cohort had a metabolic acidosis diagnosed. Metabolic acidosis at the time of birth is the most objective assessment available for the presence of fetal asphyxia (ACOG, 2006; Graham et al, 2008) and so is included in the ACOG criteria for identifying intrapartum hypoxia. However, metabolic acidosis alone is not an accurate indicator of fetal condition or neonatal outcome. Studies have found that it is the combination of metabolic acidosis with other abnormal clinical parameters of fetal and neonatal condition, such as low Apgar scores and neonatal encephalopathy that are strongly predictive of adverse outcome (Portman et al, 1990; Perlman & Risser, 1996; ACOG 2003).

Although as a stand-alone indicator it is of limited value, the analysis and recording of blood gas analysis does provide a vital piece of information in constructing an overall picture of both fetal and neonatal condition. In this cohort, 38% (n=38) had umbilical cord blood samples taken at birth, 20% (n=20) had a blood gas taken in the neonatal unit and 42% (n=42) of babies who went on to subsequently develop cerebral palsy did not have any blood gas analysis recorded. Of the 58 (58%) who did undergo blood gas analysis, only 17 (17%) had a metabolic acidosis defined as a pH<7 and BD ≥ 12 mmols. Evidence of the presence, or absence, of metabolic acidosis may be very important if the case becomes the subject of a clinical negligence litigation claim. It should, be noted of course, that metabolic acidosis is not always of intrapartum origin. It may be related to an antenatal factor such as intrauterine growth restriction, maternal diabetes or placental infarctions. Clinical practices around the sampling of newborns at birth for blood gas values vary from unit to unit. Some units limit analysis to selected neonates who are considered high risk but in many units there are no clinical guidelines available for staff and in some units the equipment necessary is not available. This situation will have to be clarified, as currently, metabolic acidosis is regarded as one of the more objective assessments of fetal asphyxia available and so may be a vital part of the puzzle in determining how an adverse outcome happened. The clinical manifestation of the neurological dysfunction following significant intrapartum asphyxia is neonatal encephalopathy.

The presence and severity of neonatal encephalopathy is considered the strongest neonatal predictor of cerebral palsy. Neonatal encephalopathy is a condition known to affect term (> 37
weeks gestation) and near term (34-37 weeks) infants. Badawi et al (2005) found that nearly 1 out of every 4 children (25%) with cerebral palsy had evidence of encephalopathy in the newborn period. In this cohort, 19% (n=19) of the babies experienced neonatal encephalopathy. The aetiology of neonatal encephalopathy is heterogeneous and it is important to distinguish neonatal encephalopathy associated with intrapartum hypoxia from that associated with antenatal factors such as nervous system anomalies, antenatal stroke, drug exposure, metabolic and genetic disorders. Sarnat’s clinical classification for the staging of neonatal encephalopathy was used in this study to diagnose encephalopathy. However, many of the medical records accessed did not document clear statements about the grading of encephalopathy. The retrospective nature of the study posed difficulties as inconsistent grading was encountered and in a number of cases the term birth asphyxia was used interchangeably with encephalopathy. However, where information about encephalopathy was vague or unavailable, the researcher was able to find information about the necessary clinical characteristics for retrospective grading (abnormal consciousness, tone, reflexes, feeding, respirations and seizures in the early days of life) by careful scrutiny of the neonatal record. Deciphering information about neonatal encephalopathy would be easier if clinicians systematically recorded the necessary information using standard terminology. It is possible that the recording of that information is better now in 2011 than it was in 1990-2000 as clinicians are now more aware of their professional and legal obligations around record keeping and of the ever-present spectre of clinical negligence litigation around intrapartum care.

Ten of the 19 cases (53%) of encephalopathy had evidence of metabolic acidosis. Metabolic acidosis was more frequent (RR 6.09 [95%CI2.66-13.92]) in the babies with neonatal encephalopathy than those without. Nine (47%) of the 19 cases of encephalopathy did not have evidence of metabolic acidosis. Of those nine, four were considered to have a prenatal cause for their encephalopathy. The other 5, although they did not fulfil the criteria for metabolic acidosis, were found to have evidence of hypoxic ischaemic encephalopathy on neuro-imaging. Closer inspection of the data collected on those particular 5 children raises some questions about the definition of metabolic acidosis. The criteria used for this study to diagnose metabolic acidosis was a pH<7.0 and a BD≥ 12mmols. This is the criteria broadly advocated in the current literature, although not everyone agrees. Among the 5 children who did not meet the stringent criteria for metabolic acidosis, 3 had pH less than 7.1 (7.01, 7.02, 7.08) and the other 2 had pH less than 7.2 (7.17, 7.18). All 5 had BD ≥ 12 (13, 13, 16, 16 and 17 respectively). Therefore, although the children did not meet the stringent criteria, they appear to have some features of metabolic acidosis on blood gas analysis. This raises some questions about the reliability of the criteria for the definition of metabolic acidosis currently advocated. It also raises some questions about the inclusion of that criterion in the ACOG (2003) international criteria for the identification of acute intrapartum hypoxia.

Studies have identified a number of illnesses in the neonatal period that are associated with cerebral palsy. Studies have also found that those illnesses differ for term and preterm babies. This study has similar findings as outlined in Tables 4.9 and 4.10 in chapter 4. Sixty-three (63%) of the babies were admitted to the neonatal unit and they experienced a number of illnesses that have
been identified in the literature as being associated with cerebral palsy. Among the term babies, those illnesses were neonatal seizures and meconium aspiration. Among the preterm babies, those illnesses were neonatal sepsis, hypotension, patent ductus arteriosus, prolonged ventilation, blood transfusion, chronic lung disease and necrotising enterocolitis. These cardiovascular, respiratory and immune system complications are common in the preterm baby and are associated with the overall immaturity of the baby. Many of these neonatal illnesses are also associated with PVL in the premature baby and PVL is well recognised as an important antecedent to cerebral palsy. All 19 cases of PVL occurred in preterm babies.

The difficulty with PVL in the causal pathway between prematurity and cerebral palsy is that the PVL may result from an ischaemic insult in utero leading to both prematurity and periventricular damage. Alternatively, the PVL may be due to an episode of blood pressure instability in the neonatal period leading to cerebral haemorrhage and ischaemic injury (Boxwell, 2000). It may also be a combination of both an antenatal and a neonatal insult (Ferriero, 2004; Bax et al, 2006; Krageloh-Mann & Horber, 2007). Case-control studies have succeeded in identifying risk factors for cerebral palsy in preterm babies. Research now needs to focus on separating antenatal factors associated with prematurity and cerebral palsy from neonatal factors associated with prematurity and cerebral palsy. In the meantime, care providers must work in a multidisciplinary manner to prevent prematurity where possible, manage the birth and resuscitation of the baby when prematurity is inevitable and continue to provide expert care to mitigate the effects of prematurity and its associated illnesses in the neonatal period.

In summary, the neonatal sample in this cohort has similar demographic characteristics to the neonatal samples in other cerebral palsy cohorts. The babies in this cohort experienced similar perinatal and neonatal factors associated with cerebral palsy as those previously identified in the literature in other cerebral palsy cohorts.

5.4 Cerebral Palsy Subtypes and Associated Impairments

The subtype distribution among children in this sample did not differ from that reported in similar studies in other jurisdictions (Table 5.3). Variance in the subtype distributions between databases is possibly due to variations in the methods used to classify subtypes and heterogeneity in the populations studied. These difficulties with variance have been reduced significantly in Europe over the last decade with the widespread use of SCPE definitions and classifications, which enables comparison of data across a number of geographical databases. Classification of cerebral palsy subtypes is important because different manifestations of cerebral palsy may reflect different aetiologies. Differences in the distributions of subtypes may be due to inter-observer variation when applying the classification criteria. However, it may reflect true differences related to birth-weight distribution in the cohort. Distributions of subtypes in this study of 84% spastic (including hemiplegia, quadriplegia and diplegia), 10% dyskinetic and 6% ataxic are broadly similar with other studies, which demonstrate that spastic cerebral palsy accounts for approximately 80% of all
Epidemiological studies have shown that the distribution of cerebral palsy subtypes varies according to gestation and this was found to be the case in this study. Spastic diplegia is the cerebral palsy most commonly associated with preterm birth and is the commonest form of cerebral palsy found among extremely premature infants (Marlow, 2006). Of the 26 cases of spastic diplegia in this study, 18 (69%) were found in the preterm subgroup giving a risk ratio (RR) of 3.52 [95% CI 1.70-7.30] for the occurrence of spastic diplegia in the preterm group. Spastic diplegia is the most commonly described long-term motor sequelae of periventricular leucomalacia (PVL). PVL is correlated highly with prematurity and accounts for the predominance of spastic diplegia in the preterm infant. In this study, of the 18 preterm children with a spastic diplegia, 12 (67%) had a diagnosis of PVL on their MRI scan. Diffuse PVL can also lead to spastic quadriplegia. This is demonstrated in this study where 7 (64%) of the 11 preterm children with a spastic quadriplegia subtype had PVL on neuro-imaging.

Spastic hemiplegia is the cerebral palsy subtype found most commonly among term children (SCPE, 2000). Of the 34 cases with spastic hemiplegia in this cohort, 29 (85%) occurred in term babies. This gives a RR of 3.71 [95% CI 1.57-8.76] for spastic hemiplegia among term babies. Hemiplegia was found to be the least disabling subtype of cerebral palsy. Thirty-two (94%) of the 34 children with spastic hemiplegia were able to walk. Analysis of the additional impairments showed that the occurrence of epilepsy (RR 0.57 [95% CI 0.32-1.01]), profound/severe intellectual impairment (RR 0.16 [95% CI 0.05-0.49]) and the inability to walk (RR 0.08 [95% CI 0.02-0.31]) were all less frequent in the spastic hemiplegic subtype than the other subtypes.

The proportion of spastic quadriplegia was similar across gestational age groups with 54% (n=13) of spastic quadriplegia occurring in the term subgroup and 46% (n=11) in the preterm subgroup (RR 0.76 [95% CI 0.38-1.51]). Spastic quadriplegia is the most disabling of the cerebral palsy subtypes. The occurrence of epilepsy (RR 2.41 [95% CI 1.64-3.52]), profound/severe intellectual impairment (RR 4.55 [95% CI 2.92-7.09]) and the inability to walk (RR 2.74 [95% CI 2.02-3.72]) were all significantly more frequent in the spastic quadriplegic subtype.

The non-spastic varieties of cerebral palsy such as dyskinetic or ataxic are more frequent in term than preterm infants (Rosenbloom, 1994; Himpens et al, 2008). While there were more term babies with dyskinetic cerebral palsy (n=6) than preterm (n=4) among children in this sample, the
difference in proportions was not significant (RR 0.96 [95%CI 0.29-3.18]). Of those infants with ataxic cerebral palsy, 5 (83%) were term and 1 (17%) was preterm (RR 3.2 [95%CI 0.39-26.34]). Both dyskinesia and ataxia are cerebral palsy subtypes with low prevalence. This means that the numbers in the cohort are very small thus making it difficult to conduct meaningful statistical analyses on the data concerning these two subtypes. Himmelmann et al (2009) reviewed the data on dyskinetic cerebral palsy in the SCPE database. They found that it occurred mainly in children born at term as was found in this cohort study. Himmelmann et al (2009) also found that dyskinetic cerebral palsy was associated with adverse perinatal events including intrapartum hypoxia. Four (40%) of the 10 children with a dyskinetic subtype in this cohort had been classified as having an adverse perinatal event at term. Himmelmann et al (2009) acknowledge the difficulties they encountered in analysing the data because of the small numbers of children and also because of a traditional lack of harmonisation of data across the contributing databases. Dyskinetic cerebral palsy is particularly disabling and 60% (n=6) of the children with dyskinesia in this study had no independent walking.

Many children with cerebral palsy have impairments other than the motor impairments that compound their condition. These additional impairments reflect brain injury beyond the motor tracts. The typical co-morbidities are visual, hearing, intellectual and feeding difficulties and were distributed in this cohort as outlined in chapter 4. Childhood epilepsy, in the form of on-going seizure activity, is the most common co-morbidity and was found in 44 (44%) of children in this cohort. Children born at term are more likely than those born preterm to have childhood epilepsy (RR 1.37 [95%CI 0.84-2.24]). This is because cerebral injury in the preterm infant is inclined to be restricted to the more vulnerable intraventricular and periventricular areas of the brain whereas term infants are inclined to have more extensive brain injuries. Hypoxic ischaemic encephalopathy following intrapartum hypoxia is also a condition of the term infant that increases the risk of a more extensive brain injury in children with cerebral palsy. The occurrence of additional impairments in this study cohort is similar to those reported by other databases as can be seen here in table 5.4.

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<tbody>
<tr>
<td>Hearing</td>
<td>5%</td>
<td>0%</td>
<td>4%</td>
<td>3%</td>
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<tr>
<td>Visual</td>
<td>14%</td>
<td>11%</td>
<td>10%</td>
<td>11%</td>
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<tr>
<td>Profound intellectual</td>
<td>39%</td>
<td>31%</td>
<td>31%</td>
<td>41%</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>44%</td>
<td>21%</td>
<td>25%</td>
<td>38%</td>
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</table>

Among the cohort, many of the children had multiple additional impairments with the number increasing as the severity of motor impairment increased. Typically, children with the most severe cerebral palsy subtype, spastic quadriplegia, experience the greatest proportion of severe additional impairments (Shevell et al, 2009). Among the 24 children in this cohort with spastic quadriplegia, 96% (n=23) had a severe/profound intellectual disability and 79% (n=19) had ongoing childhood epilepsy. The presence and severity of additional impairments has important implications for planning and providing services as well as for the quality of life of the child and their
family. The children with the most severe disabilities have greater health, social and care needs. Mortality risks also increase incrementally with an increasing number of impairments. Actuaries consider the number and severity of additional impairments when calculating the life expectancy of these children. Knowledge about the prevalence and distribution of additional impairments is very important because it facilitates early identification of morbidities and enables targeting of interventions such as educational resources. This knowledge also allows health care providers to counsel families and offer prognostic information.

The presence of additional impairments has significant implications for the child’s access to services. The child’s intellectual ability will determine the type of educational services (mainstream or intellectual disability) they are eligible to access. However, if the child has a visual, hearing or speech difficulty it can be very difficult to assess their IQ. If the child subsequently needs a gastrostomy tube for feeding, their educational placement may need to be reassessed because they will then need a service that can care for a gastrostomy tube. These are just some examples of the complexity of finding services that fit the child appropriately. Anecdotally, many families report spending significant time and effort constantly ‘fighting’ for their child’s right to appropriate services. The more complex the child’s cerebral palsy subtype and associated impairments, the more complex the task of placing the child in the appropriate services. The SCPE collaboration defines the most severe cases of cerebral palsy as those unable to walk and with a profound/severe intellectual disability. Comparisons with other cerebral palsy databases found similar distributions of severe cerebral palsy as that found in this study cohort (Table 5.5).

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<tr>
<td>No independent walking</td>
<td>35%</td>
<td>33%</td>
<td>28%</td>
<td>47%</td>
</tr>
<tr>
<td>Profound/severe intellectual impairment</td>
<td>39%</td>
<td>31%</td>
<td>31%</td>
<td>51%</td>
</tr>
<tr>
<td>Combined no walking and profound/severe IQ impairment</td>
<td>28%</td>
<td>20%</td>
<td>25%</td>
<td>20%</td>
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</tbody>
</table>

In summary, the occurrence of cerebral palsy subtypes and the distribution of co-morbidities in this cohort are similar to that described in other populations.

### 5.5 Cerebral Palsy Aetiology

The aetiology of cerebral palsy in this cohort was classified by the likely time of origin. Knowledge about the likely time of origin is helpful when trying to establish risk factors or planning preventative measures. Concepts about the origins of fetal and neonatal cerebral damage and cerebral palsy are based on neuro-pathological, radiological and epidemiological evidence (Gaffney, 1995). When classifying the aetiology of the cohort for the WICPR, the timing of the cerebral damage was determined from clinical events in the maternal and neonatal records, the cerebral palsy subtype and associated impairments and neuro-imaging findings (Mongan, 2006). Advances in technology have provided a range of imaging modalities, which have been instrumental in defining patterns of injury and providing information relating to the timing of injury in children with cerebral palsy (Truwit
The availability of such imaging in 100% of cases was instrumental in assigning aetiology in this study. Imaging modalities are constantly evolving and providing more accurate diagnosis. The greater precision of these newer modalities will enhance our understanding of injury development and individual intrinsic vulnerabilities. Further studies are needed to confirm the predictive ability of neuro-imaging. Multi-centre studies with radiologists blinded to outcomes could verify the ability of neuro-imaging to predict the timing and cause of the neuropathology in cerebral palsy cases. Such studies could also test the correlation of neuro-imaging findings with motor outcomes in children with cerebral palsy. The availability of the cerebral palsy registers could provide a sampling frame for these studies.

Latest developments in 3-dimensional and 4-dimensional ultrasound scanning have enabled the direct visualisation of fetal behaviour in-utero. It has been suggested that the assessment of fetal behaviour in different periods of gestation may make possible the distinction between normal and abnormal brain development, as well as the early diagnosis of structural or functional abnormalities (Kurjak et al, 2010). Studies into fetal behaviour as an indirect measure of central nervous system function and their predictive ability for outcome are in their early stages but may become very important in our ability to understand the origins of cerebral palsy and to predict its occurrence. Advances in this area may also provide opportunities for early intervention and harm reduction. Future studies into cerebral palsy should include data provided by these advanced imaging modalities in combination with haematological, clinical, pathological and epidemiological information.

Cases on the WICPR were classified by likely time of origin into antenatal, term perinatal, preterm, neonatal/post neonatal and unclassifiable as outlined previously in table 4.19 in chapter 4. The timing of the cerebral insult in relation to the stage of fetal and neonatal development will determine the type of injury that ensues. The likely time of origin is important because it influences the cerebral palsy subtype and the severity and type of additional impairments affecting the child with cerebral palsy.

Unclassifiable aetiology:
In 13 cases (13%) it was not possible to determine aetiology. This is a relatively low rate of unclassifiable cases. Himmelmann et al (2007) report an unclassifiable rate of 27% among Swedish children with cerebral palsy. The retrospective examination of clinical records combined with the availability of neuro-imaging for all 100% (n=100) of the children in this study may account for the ability to confirm aetiology in 87% of cases. Magnetic resonance imaging (MRI) was available for 50% (n=50) of cases, computerised axial tomography for 49% (n=49) and cranial ultrasound for 1. MRI scanning has facilitated greatly the identification of patterns and location of cerebral damage, which helps determine aetiology. It is possible that some of the 13 (13%) unclassifiable cases may have genetically determined disorders, which may become identifiable with future advances in genetics. They may also have abnormalities of cerebral development, which are not obvious immediately with currently available neuro-imaging techniques.
Antenatal aetiology:
The antenatal period was the most likely time of origin of cerebral palsy with 38% (n=38) of the cohort classified as having an antenatal aetiology. This is in keeping with current opinion that the majority of cerebral palsy is associated with antenatal factors (Stanley et al, 2000). Among the antenatal aetiology group, vascular insults (n=17, 45%) and genetic conditions (n=10, 26%) accounted for the majority of cases. The remainder of the antenatal aetiology group were due to congenital abnormalities (n=5, 13%), cerebral malformations (n=4, 11%) and cytomegalovirus (n=2, 5%). Spastic hemiplegia was the cerebral palsy subtype most commonly associated with an antenatal aetiology (RR 1.45 [95%CI 0.85-2.49]). This reflects the predominance of vascular insults within this group, as hemiplegia is the cerebral palsy subtype most commonly found following vascular insults (Reid et al, 2010). The increased use of sophisticated neuro-imaging has enabled the identification of vascular insults. Severe walking impairment was found to be less frequent (RR 0.75 [95%CI 0.42-1.35]) in the antenatal aetiology subgroup. The data analysis also revealed that the occurrence of epilepsy (RR1.19 [95%CI 0.77-1.84]) and profound/severe intellectual impairment (RR1.14 [95%CI 0.69-1.86]), was not significantly more frequent in the antenatal aetiology subgroup. This reflects the predominance of the hemiplegic subtype in the antenatal aetiology group as these children have the least severe mobility difficulties and the least severe additional impairments.

The difficulty for providers of maternity care is that most antenatal causes of cerebral palsy are currently undetectable during routine antenatal care and no randomised controlled trials have yet shown that any form of antenatal testing will decrease the incidence of cerebral palsy (ACOG, 2003). It is important that future studies focus on emerging evidence related to antenatal risk factors associated with cerebral palsy so that pregnancies with risks can be identified and managed appropriately and so that risk factors that predate labour and birth are recognised as such. Antenatal monitoring is instrumental in identifying the fetus at risk of unfavourable outcome as early as possible in pregnancy. Care must continue to focus on the reduction or elimination, where possible, of modifiable risk factors for increased risk of cerebral palsy, such as infection or prematurity. Studies have identified inflammatory markers (platelet activating factor, tumour necrosis factor, interleukin and cytokines) that are mediators of CNS pathology (Wu & Colford, 2000; Wu et al, 2003). Further studies are now needed to develop reliable, readily available, user friendly tools for identifying these markers in pregnancy. The evaluation of the fetus in utero is notoriously difficult. The development of more sophisticated investigations, such as genetic studies, karyotyping and biochemical measures will enhance our ability to recognise individual causative factors. Well designed randomised controlled trials are needed to examine whether altering the management of pregnancies with known antenatal risk factors affects the likelihood of cerebral palsy.

This study found that 45% of the antenatally acquired cerebral palsy was associated with vascular episodes. The identification of vascular insults through enhanced neuro-imaging in children with cerebral palsy has focused research on inherited and/or acquired thrombophilia in the mother and/or the baby. There is limited evidence to date around the association of thrombophilic factors
with cerebral palsy but research is ongoing as it is becoming more apparent that antenatal vascular insults are making a significant contribution to the group of cerebral palsy cases with their origin in the antenatal period (Redline, 2005; Gibson et al, 2005). Large multi-centre studies need to be conducted among mothers with a history of fetal loss and/or pre-eclampsia to test for coagulation abnormalities. Studies are needed to measure the frequency of Factor V Leiden and prothrombin mutation, which have been found to be associated with fetal and neonatal stroke (Halliday et al, 2000). Factor V Leiden and prothrombin mutation are the most common inherited thrombophilias and 15% of the western population are affected by inherited thrombophilias (Redline, 2005; Gibson et al, 2005). In Ireland, antenatal screening in pregnancy does not currently include coagulation abnormalities and collaborative studies between haematology and maternity services are needed to determine whether it should be included.

Studies need to be conducted of babies born to women with a variety of thrombophilias to establish the associated risk of stroke and/or cerebral palsy. Routine neonatal blood spot analysis for coagulation abnormalities has been advocated by some. Analysis of the placenta for signs of infarcts will be instrumental in exploring this causative pathway. The placenta could provide very valuable information regarding the intrauterine environment in terms of vascular events and inflammation associated with infection. Such placental abnormalities have been strongly associated with perinatal stroke and/or subsequent PVL, although studies are still needed to confirm the associations (McDonald, 2002; Redline, 2005). Recent research attention has focused on lesions that affect the fetal, as opposed to maternal, vascular supply including; fetal thrombosis, inflammation of fetal vessel wall and umbilical cord abnormalities (Redline, 2005). Further studies correlating placental pathology findings with neonatal outcome may prove useful. Evidence-based clinical guidelines are needed to ensure systematic in-depth examination of the placenta for histopathology in cases considered to be high risk for complications and adverse outcomes. Currently, local protocols vary and this study found that the availability of information about placental histopathology is very variable across sites. Therefore, practice guidelines are needed to highlight the practical and clinically important aspects of placental examination. As well as being a very valuable clinical resource, the availability of data from placental histopathology can be very useful in clinical negligence litigation if the cause of cerebral palsy is contentious.

Preterm aetiology:
Twenty-eight (28%) infants were classified in the preterm aetiology subgroup. It is not possible to divide clearly those children with cerebral palsy resulting from an antenatal factor contributing to their prematurity and those with cerebral palsy because of illnesses experienced during their neonatal period as premature babies. Therefore, both these perinatal and neonatal groups are classified together under the umbrella of prematurity. Spastic diplegia was the cerebral palsy subtype most commonly associated with a premature aetiology (RR 3.00 [95%CI 1.59-5.66]). Spastic quadriplegia also occurred more frequently than the other subtypes but not significantly (RR 1.29 [95%CI 0.62-2.66]). The occurrence of a severe walking impairment was found to be more frequent in the preterm aetiology subgroup (RR 1.52[95%CI 0.90-2.58]) than the other
subgroups. This is likely due to the motor impairment associated with the spastic diplegic and quadriplegic subtypes found in premature babies. This occurs because the premature brain is more vulnerable to injuries in the cerebral areas affecting the motor tracts rather than a wider area of injury affecting intellect. White matter cerebral damage in the form of PVL and IVH were found to be significantly more common in the premature aetiology subgroup (RR 29.57 [95%CI 7.46-117.24]) than the other subgroups. This is to be expected as PVL is highly correlated with prematurity. The extremely wide confidence intervals are due to the very small sample in the subgroups. The occurrence of profound/severe intellectual impairment was not significant in the premature aetiology subgroup (RR 0.89 [95%CI 0.50-1.57). This is because the preterm brain is immature, has not yet commenced rapid growth and is un-myelinated and therefore is less susceptible to global injury than the term infant. These patterns of cerebral palsy subtype and co-morbidity reflect the fact that different regions of the brain have different susceptibility to injury at different maturational stages (Ferriero, 2004).

Prematurity is a major health problem with significant neonatal ramifications as well as significant long-term consequences for childhood and is very strongly associated with cerebral palsy (Joseph et al, 2003; Platt et al, 2007; Himpens et al, 2008). Prematurity affected 6.2% of all births in Ireland in 2009, an increase from 5.3% in 2000. This study found that 39% of the children with cerebral palsy were born prematurely. Therefore, efforts must continue to prevent preterm delivery and where it is inevitable to provide antenatal interventions such as steroids and neonatal interventions such as ready access to neonatal intensive care facilities and expertise to reduce neonatal mortality and morbidity. Large trials are needed to study the use of prophylactic measures such as progesterone for the prevention of premature birth. The neuro-protective role of magnesium sulphate therapy for the preterm infant has been established through studies (Doyle et al, 2011). Further studies are now required to clarify how the magnesium sulphate works and to establish appropriate treatment regimens so that magnesium sulphate therapy can be introduced into clinical practice in Ireland.

The role of infection and chorioamnionitis in the onset of prematurity and damage to the developing fetal brain is the subject of ongoing research (Yoon et al, 2003; Tran et al, 2005). Researchers suspect that chorioamnionitis and the resulting fetal inflammatory response syndrome, mediated by pro-inflammatory cytokines, cause ischaemic brain injury in the fetus but further investigation is needed to confirm the mechanism by which this occurs. Well designed randomised controlled trials are needed to examine whether altering the management of pregnant women with known risk factors such as chorioamnionitis and infection affects the likelihood of cerebral palsy. Trials are also needed to examine whether altering the management of neonatal illnesses associated with adverse outcome in the preterm affects the likelihood of cerebral palsy. Among those illnesses are hypotension, acidosis, septic shock, patent ductus arteriosus, necrotising enterocolitis and intraventricular haemorrhages. Those of us who provide care in the neonatal units for premature babies must continue to strive to minimise those neonatal illnesses and when they do occur to manage them appropriately to mitigate both the short and long-term harm.
Clinicians and researchers must continue to collaborate in the formulation of clinical guidelines for the management of antenatal infection, prolonged rupture of membranes and preterm pre-labour rupture of membranes, all of which are risk factors for prematurity (Murphy et al, 1995; ACOG, 2003). Guidelines are also necessary to clarify the investigations recommended in a newborn where intra-uterine chorioamnionitis is suspected. High levels of cytokines and inflammatory markers have been found in cord blood, peripheral blood, amniotic fluid and the cerebrospinal fluid of these babies and studies suggest that these findings correlate with the subsequent diagnosis of cerebral palsy. Further studies are needed to better understand the relationship between chorioamnionitis, inflammation and cerebral palsy. However, consensus definitions of clinical and histological chorioamnionitis will need to be developed first. The recently established HSE National Obstetrics and Gynaecology Clinical Care Programme include the development and implementation of national clinical guidelines as one of its objectives (www.hse.ie). The findings from this study further advance the need for such national clinical guidelines by highlighting priority areas where guidelines are lacking.

Neonatal and post-neonatal aetiology:
For 5-10% of children affected by cerebral palsy, there is a clear identifiable cause in the neonatal and post-neonatal period (Stanley et al, 2000; Cans et al, 2004). Six of the children (6%) in this cohort had a cerebral palsy of post-neonatal origin. Children with a cerebral palsy of a post-neonatal origin were affected by a variety of subtypes and experienced a range of severity of impairments. Causes of the cerebral palsy among this post-neonatal group were, vascular episodes (n=3, 50%), infection (n=2, 33%) and surgical complications (n=1, 17%). Advances in vaccination programs and accident prevention initiatives mean that the post-neonatal subgroups are the aetiological group that provide the most opportunity for prevention by targeting the causative factors. As the numbers in the post-neonatal subgroup in this study were small, it was not possible to conduct any in-depth inferential analysis on them.

Perinatal aetiology:
A perinatal aetiology at term was considered responsible for cerebral palsy in 15 (15%) of cases in the cohort. Perinatal difficulty with intrapartum hypoxia, characterised by acidosis, low Apgar scores and hypoxic ischaemic encephalopathy (HIE), was considered by clinicians to be responsible for cerebral palsy in these children. These clinical signs of acidosis, low Apgar scores and encephalopathy are considered markers of a significant intrapartum episode of asphyxia. Metabolic acidosis (RR 8.10 [95%CI 3.66-17.92]), Apgar score < 6 at 5 minutes (RR15.58 [95%CI 5.71-42.54]) and neonatal encephalopathy (RR 33.30 [95%CI 9.79-113.40]) were all significantly associated with a perinatal aetiology. The wide confidence intervals are due to the small sample size in the comparison groups. Ten (66%) of the 15 cases with a perinatal aetiology at term had evidence of metabolic acidosis and 11 (73%) had Apgar scores of < 6 at 5 minutes recorded. Clinical signs of HIE, which is considered to be the best clinical indicator of an intrapartum episode of asphyxia that is currently available to clinicians, was present in all 15 cases. There are a number of potential acute catastrophic events in labour that may contribute to intrapartum injury, such as cord prolapse, shoulder dystocia and uterine rupture (ACOG, 2003). A number of obstetrical events
were experienced by the 15 cases in the perinatal aetiology group that may have been associated with the intrapartum asphyxia. Among those events were a pathological CTG in 10 cases, meconium-stained liquor in 9 cases, antepartum haemorrhage in 3 cases, pyrexia in labour in 3 cases and shoulder dystocia in 1 case. Maternity care providers must continue to receive education and skills training in order to minimise the occurrence of these risk factors and maximise their emergency response when they do occur.

Although the contribution of intrapartum hypoxia in the perinatal period among term infants to the development of cerebral palsy is infrequent, it is very significant. Children who experience a perinatal injury at term are more likely to subsequently develop a severe cerebral palsy and suffer severe additional impairments. Spastic quadriplegia (RR 2.33 [95%CI 1.17-4.64]) and dyskinesia (RR 3.78 [95%CI 1.21-11.81]) were the cerebral palsy subtypes significantly associated with this perinatal aetiology. These are the two most disabling forms of cerebral palsy. Spastic quadriplegia was evident in 7 (47%) of the 15 perinatal aetiology subgroup and dyskinesia was diagnosed in 4 cases (27%). Infants in this perinatal aetiology group were significantly more likely to have a severe walking impairment (RR 1.74 [95%CI 1.24-2.46]), severe/profound intellectual impairment (RR 1.70 [95%CI 1.03-2.81]) and epilepsy (RR 1.67 [95%CI 1.07-2.59]) than infants in the other aetiological groups. Twelve (80%) of the 15 were unable to walk, 9 (60%) had a severe/profound intellectual impairment and 10 (67%) have childhood epilepsy. This reflects the global pattern of cerebral damage resulting from an acute perinatal injury at term.

Although only a small minority of cerebral palsy is associated with intrapartum events this aetiology continues to receive significant public and professional attention because of prevailing beliefs that cerebral injury during childbirth can and should be prevented (Nelson & Grether, 1998; ACOG, 2003). Reviewing the literature revealed that there is a wide disparity of knowledge and beliefs around cerebral palsy among both professional and lay people (Hankins et al, 2003; Symon, 2002; Sartwelle, 2009). This needs to be explored further because health care professionals involved in the care and management of pregnant women and newborn babies need to be knowledgeable about cerebral palsy and its associated risk factors. They also need to be aware of the current evidence around the contribution of acute intrapartum hypoxia to the causation of cerebral palsy and the tools available for diagnosing such hypoxia. This has important implications not only for the clinical practice of such health professionals but also for the information they impart to users of the maternity services. Therefore, studies are needed among health care professionals to establish whether or not their knowledge and beliefs around cerebral palsy, its associated risk factors and its aetiology are current. Education and information programmes could then be put in place as part of their ongoing continuous professional development to address any knowledge deficits identified by such research. There is also a need to educate and inform the wider public and the legal profession about current thinking around cerebral palsy and the very small contribution of intrapartum hypoxia to causation thereby ensuring that only appropriate cases reach litigation. Knowledge and understanding of cerebral palsy is constantly evolving so ongoing initiatives to keep relevant people up-to-date are necessary now and into the future.
Although it is now accepted that intrapartum events are an infrequent cause of cerebral palsy, it is still argued often in clinical negligence litigation cases that the cause of a baby's cerebral palsy was acute intrapartum asphyxia which could, and should, have been recognised earlier when the neuropathological process was still reversible and preventable (Strijbis et al, 2006). Because the intrapartum period includes labour and birth, there is a widely held perception that different intrapartum management, such as quicker response to CTG abnormalities and expedient delivery, could prevent this group of cerebral palsy. Indeed, many members of the public believe that it should be prevented and this belief gives rise to the many clinical negligence litigation cases that result from perceived intrapartum injury in cerebral palsy cases. This is despite the fact that there is currently no convincing evidence of the effect of different intrapartum management strategies on the prevention of cerebral palsy (Young et al 2001; Nelson, 2003). In any event, because many of the current markers at our disposal for measuring intrapartum fetal and immediate neonatal status (CTG, Apgars) do not consistently accurately reflect intrapartum asphyxia, it is very difficult to identify which babies could have benefited from having their intrapartum management altered. The challenge in assigning intrapartum hypoxic aetiology is the lack of a clear and definitive definition of and method of diagnosing birth asphyxia and intrapartum hypoxia. The ACOG (2003) objective criteria for the identification of acute intrapartum hypoxia attempted to address these difficulties by providing a tool that would definitively identify babies who had experienced an acute perinatal event. This study tested the utility of the ACOG criteria in practice.

5.6 Retrospective Application of the objective criteria for the identification of acute intrapartum hypoxia

Despite the existence of these criteria since the first version in 1999 (MacLennan, 1999) and the updated version of 2003 (ACOG, 2003) there is little reference in the literature to their use in practice. Korst et al (1997, 1999) applied the criteria in a study in California and Strijbis et al (2006) applied it in Australia. Otherwise, there are no records of any attempts in Europe to use the criteria. In this study, the ACOG criteria were applied to a group of Irish cerebral palsy children who had been diagnosed as having a perinatal aetiology at term. Based on clinician assessment, perinatal difficulty with intrapartum hypoxia, characterised by acidosis, low Apgar scores and hypoxic ischaemic encephalopathy (HIE), was considered responsible for cerebral palsy in these children. The selection of this aetiological subgroup allowed the researcher to use a study population with a well-defined intrapartum hypoxic event. The ACOG (2003) have listed clinical and biochemical markers that define an acute intrapartum hypoxic event. Those clinical and biochemical markers making up the four essential criteria are:

1. pH < 7.00 and base deficit ≥ 12 mmol/L
2. Onset of neonatal encephalopathy within 24 hours
3. Cerebral palsy of the spastic quadriplegic or dyskinetic type
4. Exclusion of other pathologies associated with cerebral palsy

The retrospective nature of this cohort study enabled the researcher to examine the records of the children in the perinatal aetiology subgroup for those clinical and biochemical markers.
Retrospective application of the ACOG criteria identified 40% of the cases known to have intrapartum hypoxia but failed to identify 60% of them. Of the 15 infants who suffered an intrapartum hypoxic event, as defined by their perinatal aetiology status, 6 (40%) satisfied all 4 essential criteria, 7 (47%) met 3 essential criteria and 2 (13%) satisfied 2 essential criteria. Therefore, the sensitivity of the application of the ACOG criteria in determining those infants who were injured during labour is only 40%. When Korst et al (1999) analysed 47 cases of definite intrapartum neurological injury, only 21% of them satisfied all the essential criteria. When the criteria was applied retrospectively in this cohort, neurologically impaired babies with evidence of intrapartum hypoxia failed to satisfy the ACOG criteria for attributing cerebral injury to the intrapartum period in 60% (n=9) of cases. These children have been diagnosed by clinician review of clinical and radiological findings as having sustained a perinatal injury related to intrapartum hypoxia. Thus, the criteria were found to be too restrictive to identify consistently all cases with an acute intrapartum hypoxia severe enough to cause the adverse neurological outcome of cerebral palsy. This finding is similar to other studies that have tested the use of the criteria (Korst et al, 1997, 1999; Strijbis et al, 2006). Analysis of the distribution of each of the essential criteria found that criteria 1 (RR 8.10 [95%CI 3.66-17.92]), criteria 2 (RR 33.33 [95%CI 9.79-113.40]), criteria 3 (RR 3.12 [95%CI 1.91-5.09] and criteria 4 (RR 39.67 [95%CI 10.02-157.07]) were all more frequent in the perinatal aetiology group than in the other aetiology groups. The large confidence intervals are due to the small samples in some of the subgroups. Individually, each of the criteria can, and has been criticised.

Blood gas analysis results were available for all 15 cases in the term perinatal aetiology group (Table 4.24). Twelve of those samples were umbilical blood taken at birth and the other 3 were neonatal samples taken within 40 minutes of birth. The pH ranged from 6.64 to 7.18 with a median of 6.9 and the base deficit ranged from 13 to 19 mmols with a median of 16. Although 10 cases (67%) met the essential criteria for metabolic acidosis, 5 (33%) did not. Of the 5 who did not meet the pH < 7 criteria, 3 had pH less than 7.1 (7.01, 7.02, 7.08) and the other 2 had pH less than 7.2 (7.17, 7.18). All five had BD ≥ 12 (13, 13, 16, 16, and 17). Therefore, while 5 of the children did not meet the ACOG criteria for metabolic acidosis, it could be argued that they did have an acidosis, albeit with parameters different to those set out by ACOG. The ACOG advocate the pH and BD criteria of 7.0 and ≥ 12 respectively, as a realistic cut off point for metabolic acidosis. However, Clements and Simanowitz (2000) refer to it as a somewhat arbitrary definition of metabolic acidosis. As pH is a continuous measure, the cut off value is chosen to manage the proportion of ‘false positives’ (unaffected cases that have a positive test) and ‘false negatives’ (affected cases that have a negative test). The lower the cut-off point chosen, the fewer the false positive results, hence the pH cut-off of 7.0. When the chosen cut off point, in this case a pH of 7.0 and a BD ≥ 12, is a prerequisite for inclusion, the cases outside the cut off will be excluded from rigorous analysis. Dear and Newell (2001) contend that insisting that there is a certain severity of metabolic acidaemia before attributing cerebral palsy to intrapartum asphyxia is unreasonable as it excludes many valid cases. This raises some questions about the reliability of the criteria currently advocated for the definition of metabolic acidosis. In this cohort, the criteria outlining the prerequisite for inclusion (a pH of 7.0 and a BD ≥ 12), excluded 33% of cases. When applied to this
cohort, the metabolic acidosis criteria failed to identify 5 (33%) of the 15 children with cerebral palsy who had an acute intrapartum hypoxia.

The ACOG essential criteria relating to the onset of neonatal encephalopathy within 24 hours was met by all 15 (100%) cases in this study. Neonatal encephalopathy is characterised by abnormalities of behaviour in the neonatal period due to cerebral damage following an intrapartum insult. Epidemiological studies suggest that acute intrapartum events should not be implicated in the aetiology of cerebral palsy in the absence of these neonatal neurological abnormalities. Because neonatal encephalopathy consists of a collection of clinical signs, it can be difficult to diagnose with consistency. This means that this criterion is often quite difficult to determine. The use of rigorous operational definitions for neonatal encephalopathy in this study enabled me to overcome those problems. Clear evidence of neonatal encephalopathy was found in the medical records of all 15 cases with a perinatal aetiology. These 15 cases illustrate that 79% of the 19 babies with encephalopathy in the overall cohort had evidence of insults acquired during the intrapartum period. This compares with a proportion of 90% reported by Cowan et al (2003) when investigating the origin and timing of brain lesions in infants with neonatal encephalopathy.

The 3rd ACOG essential criterion limits the cerebral palsy subtypes resulting from acute intrapartum hypoxia to spastic quadriplegia and dyskinesia. The spastic quadriplegic cerebral palsy subtype was present in 6 (40%) of the 15 cases and dyskinesia in 4 (27%). Thus, although 10 cases (67%) met the cerebral palsy subtype criteria, 5 (33%) did not. Two of those excluded children had a spastic diplegia and 3 had a hemiplegia. Diplegia and hemiplegia are not the cerebral palsy subtypes typically found after acute intrapartum hypoxia in the term infant. However, although uncommon, it is not without precedent. In reviewing MRI abnormalities associated with cerebral palsy, Robinson et al (2008), report two cases of diplegia associated with hypoxic encephalopathy. Martinez-Biarge et al (2011), report 2 cases with hemiplegia after hypoxic ischaemic encephalopathy. Thus, children who have in fact experienced an acute intrapartum hypoxia will not always meet essential criteria 3.

The exclusion of other pathologies (essential criteria 4) was met by 14 (93%) of the 15 cases and was not met by the 1 (7%) other. The infant not meeting essential criteria 4 was growth retarded. Of note, that infant reached full term without diagnosis of the growth retardation.

Once the essential criteria have established that a significant intrapartum hypoxia has occurred, ACOG have included 5 suggestive criteria that, if present, together suggest an acute rather than chronic event. Those suggestive criteria are:

1. Sentinel hypoxic event
2. Sudden sustained fetal bradycardia or other evidence of non-reassuring fetal status
3. Apgar scores of 0-3 beyond 5 minutes
4. Multisystem failure within 72 hours of birth
5. Evidence of acute non-focal cerebral abnormality on early imaging
Among the suggestive criteria, the Apgar score of 0-3 beyond 5 minutes was least often met. Only 4 (27%) of the 15 cases met this criterion. Although low Apgar scores may be associated with intrapartum hypoxia, only prolonged low Apgars are associated with subsequent adverse neurological outcome (Moster et al, 2001; AAP, 2006b; Kveim et al, 2001). What is not clear from the literature is what is considered a low Apgar score at 5 minutes. Some studies have used ≤ 3 at 5 minutes (Kveim et al, 2010), others < 6 (Moster & Markestad, 2007) and others < 7 (Thorngren-Jerneck & Herbst, 2001). It seems from this study that the ACOG criterion of 0-3 beyond 5 minutes does not capture the majority of babies with acute intrapartum hypoxia. If the criteria were 0-6 at 5 minutes, 11 (73%) of the perinatal aetiology group would have met the suggestive criteria and if it were 0-7 at 5 minutes, all (100%) would have met the criteria. It is possible that a prolonged low Apgar is more of an indication of the effectiveness of resuscitation than a predictor of outcome. It is also true that the allocation of an Apgar score is very subjective and inter-observer inconsistencies are common.

Critics of the ACOG criteria predicted that information about the essential criteria would frequently be missing from the medical records (Greenwood et al, 2003). Critics have advocated for parameters that can easily be retrieved by retrospective chart review (Greenwood et al, 2003). I had the benefit of both midwifery and neonatal qualifications and clinical experience. This enabled me to extract data from what were, at times, the most obscure places in the records. For example, it would be commonly believed that the obvious place to find blood gas analysis results would be in the laboratory records section of the charts. This was not often the case. Blood gas analysis results were usually found in the medical notes of the doctor attending the birth of the baby and failing that they were almost always recorded in the nursing notes in the neonatal unit. The same can be said of information concerning neonatal encephalopathy, which was recorded poorly requiring that I had to search through a mixture of medical and nursing notes to quantify the clinical parameters needed to make a definitive diagnosis of the grade of neonatal encephalopathy. It could be argued that this is a failure of documentation rather than a failure of the ACOG criteria. However, having conducted the study using 100 sets of maternal and neonatal records, although it was possible to retrieve the data for the criteria it could not be said to have been easily retrieved. Without the unique combination of both midwifery and neonatal knowledge, it would have been very difficult to locate and decipher all the required data. These records relate to the years 1990-2000. Much work has been conducted since then under the clinical governance umbrella to improve standards of record keeping so it is possible that retrieval of such data from current charts would be easier.

Studies have found limited correlation between current measures of intrapartum hypoxia, such as intrapartum fetal heart rate patterns and Apgar scores, and subsequent neurological outcome (Perlman, 1997; Nelson & Grether, 1998; Greene, 2006). Other studies have shown that markers such as acidosis and encephalopathy are associated with increased risks of adverse neurological outcome (Badawi et al, 1998; Malin et al, 2010). However, neither the strength of that association nor the duration or severity of the insult associated with the neurological damage has been established. The studies are confounded by a multitude of different definitions and criteria for hypoxia and encephalopathy. Researchers have used different clinical markers for the diagnosis of
hypoxia and hypoxic ischaemic encephalopathy making study samples heterogeneous. This makes comparisons between studies difficult. When taken individually, each of the criteria advocated by ACOG are only weakly associated with an acute intrapartum event and adverse neurological outcome. Nevertheless, ACOG believed that they had identified an appropriate combination of markers to define an acute intrapartum hypoxic event sufficient to cause cerebral palsy.

The concept advocated by ACOG of a combination of factors necessary to define an acute intrapartum event sufficient to cause cerebral palsy is similar to epidemiological concepts of causal inference. Hill’s classical 1965 epidemiological theory on causation rationalised that a finding satisfying several criteria was more likely to be causal than one that satisfied none or only a few (Rothman, 2002). Rothman’s sufficient component cause model is a conceptual framework utilised in epidemiology that outlines a minimum set of conditions or events that are sufficient for an outcome to occur (Rothman et al, 2008). With this theory of cause, no specific event, condition or characteristic is sufficient by itself to produce the outcome. Rather, the causal mechanism is a constellation of components that act in concert. However, Rothman acknowledges that many, and possibly all of the components of a sufficient cause may be unknown. Rothman’s model consists of necessary causes and complementary causes, which could be synonymous with the ACOG concept of essential criteria and suggestive criteria. However, the ACOG criteria diverge completely from the epidemiological models in suggesting that their criteria establish causation. The epidemiological models limit themselves to inferring causation.

Although intrapartum hypoxia contributes to only a small number of cases of cerebral palsy, its contribution is significant in terms of consequences in that children who experience this perinatal injury are inclined to subsequently develop severe cerebral palsy subtypes and severe additional impairments. Trying to distinguish asphyxia in labour (an acute event) causing cerebral palsy from asphyxia caused by antenatal factors (a chronic feature) is an ongoing area of research (Low, 2004; Fahey & King, 2005). Retrospective application of the objective criteria advocated by ACOG (2003) for identifying acute intrapartum hypoxia in this cohort study did not find the ACOG criteria to be a reliable predictor of adverse neurological outcome due to acute intrapartum hypoxia. Other studies from other jurisdictions have reported similar results (Korst et al, 1997; Korst et al, 1999; Strijbis et al, 2006). The sensitivity of these criteria in identifying babies who have experienced an acute intrapartum event likely to cause cerebral palsy has, and will continue to be, the subject of debate. Therefore, further developments are needed to enhance the sensitivity and specificity of tests to identify accurately acute intrapartum hypoxia sufficient to cause hypoxic ischaemic encephalopathy. Future studies need to develop more specific markers of the intrapartum insult that will enable a reliable and readily available assessment of fetal and neonatal status. The knowledge generated by such studies will be critical to the development of effective strategies for prediction, minimisation and prevention of adverse outcomes for babies. The ACOG criteria may be a useful starting point for these studies but needs further refinement to make it robust for clinical practice. Despite the limitations of the ACOG criteria, the use of consensus statements for the diagnosis of intrapartum hypoxia could help clinicians to agree on a constellation of clinical markers for the accurate diagnosis and thus would enable direct comparison between studies. However, a
substantial amount of consultation will be necessary first to agree on the reliability of various clinical markers and the appropriate combination of such markers. Because intrapartum hypoxia is a relatively rare event these studies will need to be multi-institutional to collect data on enough cases to be valid. In Ireland, the availability of the three cerebral palsy registers provides a sampling frame that would enable future retrospective studies of acute intrapartum hypoxia and associated adverse outcomes. Ongoing Irish research currently taking place in a number of neonatal units studying the effects of selective hypothermia on hypoxic ischaemic encephalopathy provides an ideal opportunity for collaboration with researchers interested in cerebral palsy. As a concept the ACOG criteria are useful but need further refinement to include parameters such as modern neuro-imaging, umbilical cord lactate measurements and nucleated red blood cell measurements.

5.7 Limitations of this Study

There are some limitations of this study that must be acknowledged. The number of cases in the sample is relatively small. However, as the worldwide prevalence of cerebral palsy is only between 2 and 2.5 per 1,000 live births, only a limited number of cases exist and therefore, geographical cohorts of cerebral palsy tend to be small. Other papers have reported similarly relatively small samples. A paper by Sigurdardottir et al (2009) describing cerebral palsy in Iceland refers to a cohort of 71 children born 1990-1996. An Italian paper by Di Lallo et al (1996) discusses 89 cases on their cerebral palsy register. As the West of Ireland register is only one of three Irish registers, it is inevitable that the sampling frame is limited.

This study used a purposive sampling design which can present difficulties with generalisation to the wider population. Purposive sampling was necessary for this study to enable targeting of a population with a known experience (cerebral palsy) and so the findings are limited to this West of Ireland population. However, comparative data in the literature, describing children with cerebral palsy from other jurisdictions, shows that this West of Ireland sample is similar to others.

To minimise selection bias, observational studies need a high participation rate. The need for individual informed consent from each potential participant had the potential to limit participation rates in this study. Obtaining individual consent from participants in this study did pose major logistical challenges and consumed a significant amount of the time dedicated to the project. However, the various techniques (described previously in section 3.5.5) employed to enhance response rates achieved a response rate of 79% which is a high participation rate following a postal request (Kelly & Long, 2000). Notwithstanding the small sampling frame and the 79% response rate, the use of a sample size calculator (section 3.5.4) indicated that the final sample of 100 participants was appropriate to provide results that could confidently be said to represent the target population.

The study is limited by its retrospective design. Data that are obtained by retrospective review of medical records are prone to inaccuracies due to incomplete records or misinterpretation of
information. In this study these potential limitations were addressed by careful scrutiny of extensive medical and midwifery records and the use of detailed operational definitions in the data extraction form. My unique combination of both midwifery and neonatal clinical experience facilitated me extracting and abstracting data from the records.

Despite these limitations, all findings compare favourably with data reported from other cerebral palsy databases (SCPE, 2000; Parkes et al, 2005; Sigurdardottir, 2009).

5.8 Conclusion

This chapter has discussed the main issues arising from the findings of the study in the context of the broader literature and evidence base. The limitations of the study are acknowledged. This study found that the prevalence of cerebral palsy, characteristics of the maternal and neonatal cohort and the distribution of subtypes, co-morbidities and aetiologies were similar to those described in other populations in other jurisdictions. Maternal and neonatal data demonstrate that the study cohort experienced antenatal, intrapartum and neonatal factors associated with cerebral palsy similar to those described in other populations. Retrospective application of the ACOG criteria for acute intrapartum hypoxia yielded results similar to those of other studies. Cases with evidence of acute hypoxia failed to satisfy consistently the four essential ACOG criteria required to attribute causation of their injury to the intrapartum period.

Cerebral palsy is a complex condition that can vary in aetiology, manifestations, co-morbidities, severity and prognosis. Current thinking supports the opinion that cerebral palsy arises from a combination of associated factors and intrinsic vulnerabilities. Only a minority of cases have a known cause although decades of worldwide epidemiological studies have isolated dozens of cerebral palsy risk factors. However, risk factors are not causes; they represent associations. There are relatively few modifiable risk factors for cerebral palsy. A fundamental problem in efforts to prevent cerebral palsy is the limited understanding of its causation. Sartwell (2009:206) points out that the problem with cerebral palsy is that there is no objective test available to screen for the condition, nor is there a gold standard test that absolutely makes the diagnosis. This study found that within the sample of 100 cases there were a variety of identifiable antenatal, intrapartum and neonatal risk factors associated with a variety of cerebral palsy subtypes and associated co-morbidities. The study demonstrated that certain intrinsic vulnerabilities in the babies did influence the outcome. For example, the gestational age at birth influenced the cerebral palsy subtype with the preterm babies having a predominance of diplegic cerebral palsy and the term babies most commonly having a hemiplegic cerebral palsy.

Despite advances in perinatal medicine, intrapartum care and neonatal care the frequency of cerebral palsy remains unchanged over the last 25 years at 2-2.5/1,000 live births. Most cases of cerebral palsy cannot be prevented by current available methods of monitoring and management. Historically, birth trauma or birth asphyxia was thought to be the origin of cerebral palsy. In spite of the availability of numerous studies showing that lack of oxygen does not cause cerebral palsy except in a tiny minority of cases, the ‘lack of oxygen theory’ continues to receive much
professional, litigious and public attention. It is now known that there are many causes of cerebral palsy including developmental abnormalities, metabolic conditions, autoimmune and coagulation disorders, infections, trauma and hypoxia in the fetus and the newborn. Epidemiological studies suggest that in about 70-80% of cases acute intrapartum hypoxia is not the cause of cerebral palsy. In the remaining 10-20%, difficulty persists in determining the diagnosis of intrapartum hypoxia and its contribution to cerebral palsy. In this study 15% of cases were considered to be associated with intrapartum hypoxia but difficulty with determining that diagnosis was encountered when the ACOG criteria for the identification of acute intrapartum hypoxia was used. The ACOG criteria for the identification of acute intrapartum hypoxia identified only 40% (n=6) of the 15 cases who were considered by clinicians to have a cerebral palsy aetiology associated with intrapartum hypoxia.

The issue of cerebral palsy causes and clinical culpability remains contentious. The human and financial costs of cerebral palsy continue to be extremely high so it is imperative that collaborative efforts among paediatric, neurological, radiological, pathological, obstetric and midwifery providers continue in an attempt to better understand and manage this condition and continue efforts to ultimately prevent it. The following chapter offers some recommendations for such collaborative efforts.
Chapter 6
Conclusions and Recommendations

6.1 Introduction
This chapter will present the main conclusions arising from this study based on the findings of this study in the context of the wider literature base. Recommendations will be made in relation to the implications of the study for practice, education, policy and further research. The significance of the study will be considered from the perspective of:

- Ways in which the study adds to the scholarly research and literature in the field;
- Ways in which the study helps to improve practice;
- Reasons why the study will improve policy;
- Importance of the study for researchers, practitioners and policy makers.

6.2 Thesis summary
There is an abundance of literature on cerebral palsy in general, an increasing amount on cerebral palsy in Europe, but very limited publications on cerebral palsy in Ireland. Although cerebral palsy registers are identified as a key component in delivering an effective and efficient service, there is a dearth of publications relating to the Irish cerebral palsy registers. Having reviewed the literature on cerebral palsy for this Irish study, it is obvious that cerebral palsy is a complex condition that is heterogeneous in both its manifestations and its causation. The nature and timing of events in the causal pathway leading to cerebral palsy remains unclear in many cases. Decades of research have found that cerebral palsy has many associated risk factors. It is now accepted widely that 70-80% of cerebral palsy cases are associated with antepartum risk factors and causal pathways, 5-10% have a clear identifiable cause in the neonatal and post neonatal period and the proportion of cerebral palsy that can be attributed to intrapartum events is now estimated to be approximately 6-10% (Stanley et al, 2000).

Having identified the associated factors through research, further studies are now needed to help in defining and understanding the causation of cerebral palsy, which may lead eventually to clinical interventions that will reduce the rates. There is a persisting lack of consensus around the role of acute intrapartum hypoxia in association with cerebral palsy and also around the identification and correct diagnosis of acute intrapartum hypoxia. Although acute intrapartum hypoxia is often implicated in the causal pathway to cerebral palsy, there is limited research examining the criteria put forward by ACOG (2003) for defining acute intrapartum hypoxia sufficient to cause cerebral palsy. There are no previously published research studies examining the application of the ACOG criteria in a European context.

The aim of this study therefore was to describe the prevalence, distribution and interrelationships of antenatal, intrapartum and neonatal variables associated with cerebral palsy and apply the objective criteria for the identification of acute intrapartum hypoxia in a cohort of children with
cerebral palsy. This retrospective cohort study employed a survey approach gathering data through use of a questionnaire. Following identification of the sample from the West of Ireland Cerebral Palsy Register (WICPR), data were collected by retrospective extraction and abstraction from maternal and neonatal hospital records. Data sought related to the prevalence, distribution and inter-relationship of variables associated with cerebral palsy.

Possible limitations of this study are acknowledged as the small sample size, the use of a purposive sample, the need for consent to access medical records and the collection of retrospective data, all of which have been addressed, including methodological approaches to minimise their impact, in chapter 3. This study presents, for the first time, a comprehensive picture of cerebral palsy in a cohort of Irish children and tests the ACOG criteria in practice in an Irish setting.

6.3 Summary of findings
The prevalence, distribution and interrelationships of antenatal, intrapartum and neonatal variables associated with cerebral palsy are described and the application of the objective criteria for the identification of acute intrapartum hypoxia in a cohort of children with cerebral palsy examined. This study does not claim to present a complete view of the cerebral palsy population of Ireland but the findings contribute to the paucity of literature in the area by describing the cerebral palsy population in one of three geographical areas. The study concludes that this cohort of children have a distribution of antenatal, intrapartum and neonatal factors associated with cerebral palsy similar to that found in other populations of children with cerebral palsy. The children have a distribution of cerebral palsy subtypes and associated impairments similar to other cohorts of children with cerebral palsy. The finding that the ACOG criteria was deficient in identifying acute intrapartum hypoxia sufficient to cause cerebral palsy is also similar to that found in other populations of children with cerebral palsy. The use of the cerebral palsy register in the West of Ireland to provide a sampling frame for this study, in addition to providing important information about cerebral palsy subtypes and associated impairments, illustrates clearly the immense value of such registers. Mulhall (1996) acknowledges that value when she points out that there is simply no value to collecting epidemiological data on a register that are not regularly analysed, interpreted and disseminated to those who need them. The study also found that epidemiology, although traditionally associated with the medical profession, is a research methodology conducive to illuminating areas of interest and value to nurses and midwives.

6.4 Recommendations
In order to develop and enhance our understanding of cerebral palsy and acute intrapartum hypoxia as an associated risk factor, further detailed study is required. Based on the findings and conclusions of this research study the following education, practice, policy and research focused recommendations are made in order to benefit the children living with cerebral palsy, their families, the professionals who provide them with services and researchers who continue to strive to
understand cerebral palsy and minimise its occurrence and impact. These recommendations relate to questions raised by the study that require further exploration and/or action.

- It is recommended that a single, complete Republic of Ireland cerebral palsy register combining data held on the Eastern, Southern and Western registers be created;
- Maternity care must continue to focus on antenatal risk factors so that pregnancies with risks associated with cerebral palsy can be identified and managed appropriately;
- Efforts must continue to prevent low birth weight and preterm births and where they are inevitable to provide antenatal and neonatal interventions to reduce associated neonatal mortality and morbidity;
- Multiple births should continue to be the subject of close surveillance in an effort to reduce the associated mortality and morbidity, particularly cerebral palsy;
- Due to its association with cerebral palsy, delayed childbearing and the transfer of multiple embryos with fertility treatment must be addressed through education and policy initiatives;
- Studies examining health care professionals' knowledge and beliefs around cerebral palsy, its associated risk factors and its aetiology should be conducted;
- Methods of monitoring fetal wellbeing during labour that are safe, reliable, cause minimal discomfort and are acceptable to women need to be explored so that babies at increased risk of cerebral palsy may be recognised and managed accordingly;
- The ACOG criteria have not been found to be reliable in clinical practice therefore, further developments are needed to enhance the sensitivity and specificity of tests to identify accurately acute intrapartum hypoxia sufficient to cause hypoxic ischaemic encephalopathy;
- Further research is required to develop tools for the reliable and readily available assessment of fetal status as well as the development of more specific markers of an intrapartum insult;
- Further studies are needed to confirm the ability of neuro-imaging to predict the timing and cause of the neuropathology in cerebral palsy cases. Such studies could also test the correlation of neuro-imaging findings with motor outcomes in children with cerebral palsy;
- Data held by the State Claims Agency relating to cerebral cases needs to be analysed to provide a comprehensive picture of the extent of litigation associated with cerebral palsy in Ireland and possibly provide information to facilitate cost reduction initiatives;
- Nursing and midwifery curricula need to include epidemiology to a greater extent in their research methodology modules and need to encourage epidemiological studies by their undergraduate and postgraduate student population;
- Ongoing long-term follow-up studies of children with acute intrapartum hypoxia, neonatal encephalopathy and cerebral palsy are necessary for surveillance of outcomes.
6.5 Unique Contribution to Knowledge

This study provides a comprehensive picture of cerebral palsy and its associated factors from conception to childhood in a uniquely Irish cohort. It provides a significant contribution to knowledge by describing for the first time the demographics, clinical characteristics and risk profiles of children with cerebral palsy in Ireland. Specifically, for the first time, we now have data describing profiles such as gestational age and birth weight for infants with Cerebral palsy in Ireland. We now have information on the subtypes of cerebral palsy in a cohort of Irish children. Importantly, we now have information on the other impairments these children suffer in addition to their motor difficulties. We now know what proportion of infants with cerebral palsy, in an Irish setting, are likely to have suffered cerebral palsy in the ante, intra and postpartum periods and, importantly, what proportion of infants for which timing of causation has not been possible. This information allows us to benchmark our performance against other jurisdictions. We can now say confidently that a baby born in the West of Ireland has no greater risk of cerebral palsy than one born elsewhere in Ireland or Europe and no greater risk of more severe CP subtypes and additional impairments. Without this study this would not have been possible. The fact that this study finds no substantial differences in these factors is reassuring and should not detract from the unique contribution of the study. The absence of significant differences has only been identified by the conduct of this study and were this study not conducted we would have an absence of such evidence.

An additional unique aspect of this study relates to the broad overview of cerebral palsy provided by the distinctive combination of both a midwifery and neonatal perspective. Nelson (2005) advocated just such a study when she advised that studies are needed that will connect the dots, putting together maternal characteristics, neonatal state, brain imaging findings and outcomes to provide information on pathways to disability. My combination of both midwifery and neonatal clinical practice experience enabled me to combine maternal, neonatal, antenatal, intrapartum and post-natal aspects together in one single study. This facilitated the production of a comprehensive picture of cerebral palsy and its associated factors. An in-depth study of this type has not been conducted previously in Ireland.

Application of the ACOG criteria for defining acute intrapartum hypoxia in a European cohort of children is also exclusive to this study. The study tested the ACOG criteria in practice in an Irish setting. The criteria have been in existence since 1999 in its original version and its updated version in 2003 but there is little evidence in the literature of its use and applicability in clinical practice. This is the first published account of its application in a European setting. For the first time, this study demonstrates that the current ACOG criteria are not discriminating in identifying acute intrapartum hypoxia sufficient to cause cerebral palsy.
6.6 Conclusion

This chapter has reviewed the research study, its findings and the conclusions reached. The implications of the findings and the actions necessary to bring about change have been presented in a series of recommendations. The information provided by the study will make a significant contribution to knowledge about the demographics, clinical characteristics and risk profiles of children with cerebral palsy in Ireland. The study also provides useful information about acute intrapartum hypoxia and the failure of the ACOG criteria to identify it in the cohort. The data generated by this uniquely Irish cohort study provides valuable baseline information useful in enhancing our understanding of cerebral palsy. That enhanced understanding of cerebral palsy should help to broaden the knowledge that underpins clinical practice in this area.

Decades of epidemiological studies have identified the antenatal, intrapartum and neonatal factors that are associated with cerebral palsy. This study found similar risk factors in a uniquely Irish cohort. Further studies are now needed to understand why these factors contribute to cerebral injury in some babies and not in others and whether this injury can be predicted, minimised or prevented. Such studies would be greatly enhanced by the availability of large sample groups. Those sample groups could be provided by a single national cerebral palsy register. Researchers must continue to study the impact of changes in antenatal (steroids), intrapartum (monitoring) and neonatal care (resuscitation, ventilation) on the prevalence of cerebral palsy. This study has made recommendations for some of that future research.
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Appendix 1.1
Strobe Guideline
STROBE Statement—Checklist of items that should be included in reports of **cohort studies**

<table>
<thead>
<tr>
<th>Item No</th>
<th>Recommendation</th>
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<tbody>
<tr>
<td><strong>Title and abstract</strong></td>
<td>1</td>
</tr>
<tr>
<td>(a) Indicate the study’s design with a commonly used term in the title or the abstract</td>
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<tr>
<td>(b) Provide in the abstract an informative and balanced summary of what was done and what was found</td>
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<tr>
<td><strong>Introduction</strong></td>
<td>2</td>
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<tr>
<td>Background/rationale</td>
<td>Explain the scientific background and rationale for the investigation being reported</td>
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<td>Objectives</td>
<td>3</td>
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<tr>
<td>State specific objectives, including any prespecified hypotheses</td>
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<tr>
<td><strong>Methods</strong></td>
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<tr>
<td>Study design</td>
<td>Present key elements of study design early in the paper</td>
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<tr>
<td>Setting</td>
<td>5</td>
</tr>
<tr>
<td>Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection</td>
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<tr>
<td>Participants</td>
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<td>(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up</td>
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<td>(b) For matched studies, give matching criteria and number of exposed and unexposed</td>
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<td>Variables</td>
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<tr>
<td>Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable</td>
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<td>Data source/measurement</td>
<td>8*</td>
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<tr>
<td>For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group</td>
<td></td>
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<tr>
<td>Bias</td>
<td>9</td>
</tr>
<tr>
<td>Explain any efforts to address potential sources of bias</td>
<td></td>
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<tr>
<td>Study size</td>
<td>10</td>
</tr>
<tr>
<td>Explain how the study size was arrived at</td>
<td></td>
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<tr>
<td>Quantitative variables</td>
<td>11</td>
</tr>
<tr>
<td>Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why</td>
<td></td>
</tr>
<tr>
<td><strong>Statistical methods</strong></td>
<td>12</td>
</tr>
<tr>
<td>(a) Describe all statistical methods, including those used to control for confounding</td>
<td></td>
</tr>
<tr>
<td>(b) Describe any methods used to examine subgroups and interactions</td>
<td></td>
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<tr>
<td>(c) Explain how missing data were addressed</td>
<td></td>
</tr>
<tr>
<td>(d) If applicable, explain how loss to follow-up was addressed</td>
<td></td>
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<tr>
<td>(e) Describe any sensitivity analyses</td>
<td></td>
</tr>
<tr>
<td><strong>Results</strong></td>
<td>13*</td>
</tr>
<tr>
<td>Participants</td>
<td></td>
</tr>
<tr>
<td>(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed</td>
<td></td>
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<tr>
<td>(b) Give reasons for non-participation at each stage</td>
<td></td>
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<tr>
<td>(c) Consider use of a flow diagram</td>
<td></td>
</tr>
<tr>
<td>Descriptive data</td>
<td>14*</td>
</tr>
<tr>
<td>(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders</td>
<td></td>
</tr>
<tr>
<td>(b) Indicate number of participants with missing data for each variable of interest</td>
<td></td>
</tr>
<tr>
<td>(c) Summarise follow-up time (eg, average and total amount)</td>
<td></td>
</tr>
<tr>
<td>Outcome data</td>
<td>15*</td>
</tr>
<tr>
<td>Report numbers of outcome events or summary measures over time</td>
<td></td>
</tr>
<tr>
<td>Main results</td>
<td>16</td>
</tr>
<tr>
<td>(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included</td>
<td></td>
</tr>
<tr>
<td>(b) Report category boundaries when continuous variables were categorized</td>
<td></td>
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<tr>
<td>(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period</td>
<td></td>
</tr>
<tr>
<td>Other analyses</td>
<td>17</td>
</tr>
<tr>
<td>----------------</td>
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</tbody>
</table>

**Discussion**

<table>
<thead>
<tr>
<th>Key results</th>
<th>18</th>
<th>Summarise key results with reference to study objectives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limitations</td>
<td>19</td>
<td>Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias</td>
</tr>
<tr>
<td>Interpretation</td>
<td>20</td>
<td>Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence</td>
</tr>
<tr>
<td>Generalisability</td>
<td>21</td>
<td>Discuss the generalisability (external validity) of the study results</td>
</tr>
</tbody>
</table>

**Other information**

| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based |

*Give information separately for exposed and unexposed groups.

Appendix 2.1

SCPE Decision Tree
DECISION TREE for identifying cerebral palsy

Does the child have a disorder of movement or posture?

Y  N  EXCLUDE

Does the child have a loss of motor function?

Y  N  EXCLUDE

Is the condition progressive?

N  Y  EXCLUDE

Go back and reassess after age 4

Was the child at least 4 years old when assessed?

N

Is the child still living?

Y

N

Does the child have a syndrome/brain anomaly or chromosome abnormality?

Y

N

Recheck - does the child meet the criteria for the definition of CP?

Y

N  EXCLUDE

Did the child die between the age of 2 and 4 years?

Y

N

Did the child die between the age of 2 and 4 years?

N  EXCLUDE

Does the child have generalised hypotonia?

Y

N

Look at Classification Tree - see overleaf

Ataxic CP  EXCLUDE

Are there signs of ataxia?

Y

N

Appendix 2.2
SCPE Classification Tree
CLASSIFICATION TREE for sub-types of cerebral palsy

Is there persisting increased muscle tone in one or more limbs?

Y → Are both sides of the body involved?
N → Is the tone varying?

Y → Spastic Bilateral
N → Spastic unilateral

Is the tone varying?

Y → Dyskinetic CP
N → Is there generalised hypotonia with signs of ataxia?

Y → Reduced activity - tone tends to be increased
N → Increased activity - tone tends to be decreased

Y → Dystonic CP
N → Chorea-Athetotic CP

N → Ataxic CP → Non-classifiable
Appendix 3.1
HSE Ethics Committee Approval Letter
Ms. Patricia Healy
47 Manor Grove
Mountmellick
Co. Laois.

Ref: C.A. – 265 – Describing the epidemiology of Cerebral Palsy in the West of Ireland: A Retrospective Cohort Study.

Dear Ms. Healy,

I have considered the above project, and I am happy to grant Chairman’s approval.

Yours sincerely,

Dr. Shaun T. O’Keeffe
Chairman Clinical Research Ethics Committee.
Appendix 3.2: 
NUI Galway Ethics Committee Approval Letter
Ms Patricia Healy
47 Manor Grove
Mountmellick
Co Laois

Dear Ms Healy

Re: Ethics Application: “Describing the epidemiology of cerebral palsy in the West of Ireland: a retrospective cohort study.”

I write to you regarding the above proposal which was submitted for Ethical review. Having reviewed your response to my letter, I am pleased to inform you that your proposal has been granted APPROVAL.

All NUI Galway Research Ethic Committee approval is given subject to the Principal Investigator submitting an annual report to the Committee. The first report is due on or before 31st July 2010. Please see section 7 of the REC’s Standard Operating Procedures for further details which also includes other instances where you are required to report to the REC.

Yours Sincerely

[Signature]

Dr Saoirse Nic Gabhainn
Chairperson
Research Ethics Committee
Appendix 3.3:  
Data Confidentiality Agreement
CONFIDENTIALITY AGREEMENT

Name of Database: West of Ireland Cerebral Palsy Register

As a researcher working with the research study, Cerebral palsy in the West of Ireland and the application of the international criteria for the identification of acute intrapartum hypoxia: a retrospective cohort study, I agree to be bound by the normal procedures governing patient confidentiality.

Information about individual patients will be treated confidentially and will be used solely for the purpose of the research study.

Researcher Signature: Patricia Healy  Date: 6/10/2010

Researcher Name (block capitals):  PATRICIA HEALY

Witnessed by data controller: 

School of Nursing & Midwifery
Scoil an Altranais agus an Chomhshláthais
National University of Ireland, Galway.
Galway, Ireland.
Founded in 1845

Tel: +353 91 524411 ext: 3432
Direct: +353 91 493432
Fax: +353 91 494537
Email: nursing@nuigalway.ie
Appendix 3.4:
Data Agent Nomination Form
Name of Database: West of Ireland Cerebral Palsy Register

As the data controller representing the database named above, I hereby nominate Patricia Healy, PhD student, as an agent of this database for the duration of the registers involvement in the study:

*Cerebral palsy in the West of Ireland and the application of the international criteria for the identification of acute intrapartum hypoxia: a retrospective cohort study.*

As an agent of the database Patricia Healy, PhD student, will be bound by the normal procedures governing patient confidentiality.

Information about individual patients will be treated confidentially and will be used solely for the purpose of the research study.

Patricia Healy, PhD student will remove personal identifiers from the data as soon as they are extracted from the patient records to ensure that only anonymised data is analysed for the study.

Data Controller Signature: ____________________________ Date: 6/1/10

Data Controller Name (block capitals): ________________________
Appendix 3.5:
Invitation to participate
Date

To whom it concerns,

I am writing to you regarding a proposed research study about cerebral palsy in the West of Ireland. The study will be undertaken by Patricia Healy, a midwifery PhD student with the National University of Ireland, Galway. Patricia will be conducting the study under my direct supervision and with the approval and support of Dr Kevin Dunne, Consultant Paediatrician. I enclose information about the study for your consideration.

Many thanks

Yours sincerely

[Signature]

Dr G. Gaffney, Consultant Obstetrician/ Data Controller for West of Ireland Cerebral Palsy Register.
Appendix 3.6: Reminder Letter
Reminder Letter

To whom it concerns,

You may remember my writing to you quite recently requesting your participation in a study entitled “Cerebral palsy in the West of Ireland and the application of the international criteria for the identification of acute intrapartum hypoxia: A cohort study”. I asked you to sign a consent form allowing me to access your records.

To begin my study I need at least 70 participants. So far I have consent from 55 so I still need 15 more. Therefore, I am now writing to request that if you did not complete and return your consent form that you do so at your earliest convenience or within the next two weeks please. I have enclosed another copy of the consent form and the stamped addressed envelope in case you have misplaced the original.

Although of no immediate personal benefit to you this study will provide valuable information essential to our understanding of cerebral palsy. The findings may be useful to make recommendations for ongoing management of cerebral palsy and the services provided. The information generated will also allow us to compare cerebral palsy in the West of Ireland with cerebral palsy elsewhere.

If you have already completed and returned the consent form or have decided that you do not want to participate in the study, thank you very much and please disregard this reminder.

I would like to take this opportunity to thank you most sincerely for your participation.

Yours sincerely

Patricia Healy
### Maternal Data

1. Woman’s study number:  

2. Age at booking:  

3. Gravida:  

4. Parity:  

5. Health Insurance:  
   (a) Private  
   (b) Public  

6. Maternal Socio-economic group: *(please tick one box only)*  
   (a) Farmer/ Farm labourer/ Fisherman  
   (b) Professional/ Managerial  
   (c) Intermediate non-manual  
   (d) Skilled/senior-skilled manual  
   (e) Unskilled manual/ unemployed  
   (f) Missing  

7. Woman’s agreed EDD:  

<table>
<thead>
<tr>
<th>day</th>
<th>month</th>
<th>Year</th>
</tr>
</thead>
</table>

8. Antenatal Care:  

   | Yes | 1 | No | 0 |

9. Infertility Treatment:  

   | Yes | 1 | No | 0 |

10. Maternal Thyroid Disease:  
    (a) No  
    (b) Hypothyroidism  
    (c) Hyperthyroidism  

11. Maternal seizures:  
    (a) No  
    (b) Epilepsy  
    (c) Pre-eclamptic seizure  

12. History of Maternal disease:  
    (a) None  
    (b) Renal disease  
    (c) Cardiac disease  
    (d) Haemoglobinopathies  
    (e) Antenatal Rhesus antibodies  

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Oct 2010

Page 2

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191
13. Maternal diabetes:
   (a) No 0
   (b) Pre-gestational Type 1 1
   (c) Pre-gestational Type 2 2
   (d) Gestational diabetes mellitus 3
   (d) Gestational IGT 4

14. Maternal hypertension:
   (a) No 0
   (b) Pre-gestation hypertension 1
   (c) Pregnancy induced hypertension 2
   (d) Pre-eclampsia 3

15. Bleeding after 20 weeks:
   (a) No 0
   (b) Abruption 1
   (c) Placenta previa 2

16. Antenatal Infection:  
    Yes 1  No 0

17. Pyrexia in labour:  
    Yes 1  No 0

18. Labour onset:
   (a) Spontaneous 1
   (b) Induced with Prostaglandin 2
   (c) Induced with Artificial rupture of membranes 3
   (d) Induced with syntocinon 4
   (c) Not in labour, caesarean section 5

19. Syntocinon given:
   (a) No 0
   (b) for induction 1
   (c) for augmentation 2

20. Mode of birth:
    (a) Elective c/section 1
    (b) Non-elective c/section 2
    (c) Instrumental ventouse 3
    (d) Instrumental forceps 4
    (e) Spontaneous vaginal 5

21. Breech presentation:  
    Yes 1  No 0

22. Persistent Occipitoposterior Position:  
    Yes 1  No 0

23. Acute Intrapartum Event:
    (a) None 0
    (b) Umbilical Cord Prolapse 1
    (c) Shoulder Dystocia 2
    (d) Uterine Rupture 3
    (e) Maternal Cardiopulmonary Arrest 4
    (f) Pathological CTG 5
24. Labour CTG:
   (a) Normal 1
   (b) Suspicious 2
   (c) Pathological 3
   (d) Not recorded during labour 2222

25. Meconium Stained Liquor: Yes 1 No 0

26. Duration of Rupture of Membranes:
   Hrs Mins

27. Gestation at Rupture of Membranes
   weeks Days

28. Placenta
   Normal 1 Abnormal 0
   if abnormal, type of abnormality reported:

29. Placenta sent for histology: Yes 1 No 0

---

**Neonatal Data**

1. Infant's date of birth:
   day month year

2. Infant's time of birth:
   Hrs Mins
   (Please use 24hr clock)

3. Sex:
   Male 1 Female 2

4. Gestation at birth:
   weeks days

5. Birth weight in grams:

6. Plurality:
   (a) Singleton 1
   (b) Twin 2
   (c) Triplet 3
   (d) >Triplet 4
7. Apgar Score: (as documented in birth records)
   (a) Apgar score at 1 minute
   (b) Apgar score at 5 minutes
   (c) Apgar score at 10 minutes

8. Resuscitation at birth:  
<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
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<tbody>
<tr>
<td>(a) None</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>(b) Suction</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>(c) Oxygen</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>(d) Bag and mask</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>(e) Intubation</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>(f) Chest Compressions</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>(g) Resuscitation Drugs</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

9. Cord blood:  
   | Cord blood taken at birth | Yes | No |
   |                          |     |    |
   | Results:                 |     |    |
   | pH                       | 2   | 1   |
   | BD                       |     |     |

10. Tight Nuchal Cord  
   | Yes | 1 | No | 0 |

11. Congenital Anomaly  
   | Yes | 1 | No | 0 |

   If yes, type of anomaly diagnosed:

   ........................................................................................................
   ........................................................................................................
   ........................................................................................................

12. Number of days in Neonatal Unit:  

13. Blood gas analysis:  
   Blood gas taken in neonatal unit  
   | Time of 1st NICU Gas: | Results | Venous | Arterial | Capillary |
   |                      |         |        |          |          |
   |                      | Ph      | 1      | 2        | 3        |
   |                      | BD      |        |          |          |

13A. Length of time between birth and first gas:  
   (Please use 24hr clock)  
   | Hrs | Mins |

Oct 2010
### 14. Neonatal illness:

| (a) Neonatal sepsis (positive blood culture) | Yes | No |
| (b) Hypotension | 1 | 0 |
| (c) Hypoglycaemia | 1 | 0 |
| (d) Pneumothorax | 1 | 0 |
| (e) PDA requiring medication or ligation | 1 | 0 |
| (f) Prolonged mechanical ventilation (>7 days) | 1 | 0 |
| (g) Neonatal seizures | 1 | 0 |
| (h) Blood transfusion | 1 | 0 |
| (i) Chronic lung disease | 1 | 0 |
| (j) NEC within first week of life | 1 | 0 |
| (k) Meconium aspiration | 1 | 0 |
| (l) Jaundice requiring exchange transfusion | 1 | 0 |
| (m) Thrombocytopenia/Coagulopathy | 1 | 0 |

### 15. Encephalopathy:

| (a) No encephalopathy | 0 |
| (b) Mild neonatal encephalopathy | 1 |
| (c) Moderate neonatal encephalopathy | 2 |
| (d) Severe neonatal encephalopathy | 3 |

### 16. Evidence of multisystem failure within 72 hours of birth:

| (a) Oliguria (<1ml/kg/hr) for at least 24 hrs | Yes | No |
| (b) Inability to maintain serum Na>130mmol/dl for at least 24 hrs | 1 | 0 |
| (c) Serum creatinine >1.2mg/dl for >3 days | 1 | 0 |
| (d) Platelet count <150,000 | 1 | 0 |
| (e) Mechanical ventilation for 24 hrs | 1 | 0 |
| (f) Vasopressors for hypotension for >3 days | 1 | 0 |
| (g) PPHN requiring treatment | 1 | 0 |

### 17. Cerebral radiology:

| (a) None | 0 |
| (b) Cranial ultrasound | 1 |
| (c) CAT Scan | 2 |
| (d) MRI | 3 |

### 18. Cerebral radiology result: (please record most recent)

| (a) Normal | 0 |
| (b) Dilated ventricles | 1 |
| (c) Intraventricular haemorrhage grade I | 2 |
| (d) Intraventricular haemorrhage grade II | 3 |
| (e) Intraventricular haemorrhage grade III | 4 |
| (f) Intraventricular haemorrhage grade IV | 5 |
| (g) Periventricular leukomalacia | 6 |
| (h) Cerebral oedema, ischaemia, infarcts | 7 |
| (i) Cerebral malformation | 8 |
| (j) Cerebral abnormality | 9 |
19. Known cause of CP: (please record most recent)

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<tbody>
<tr>
<td>(a)</td>
<td>Cerebral malformation</td>
</tr>
<tr>
<td>(b)</td>
<td>Prenatal vascular injury</td>
</tr>
<tr>
<td>(c)</td>
<td>Defined prenatal syndrome</td>
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<tr>
<td>(d)</td>
<td>Genetic/ familial condition</td>
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<tr>
<td>(e)</td>
<td>Congenital abnormality</td>
</tr>
<tr>
<td>(f)</td>
<td>Intrauterine infection</td>
</tr>
<tr>
<td>(g)</td>
<td>Perinatal event</td>
</tr>
<tr>
<td>(h)</td>
<td>Neonatal event</td>
</tr>
<tr>
<td>(i)</td>
<td>Post neonatal event</td>
</tr>
<tr>
<td>(j)</td>
<td>Preterm: perinatal/ neonatal</td>
</tr>
<tr>
<td>(k)</td>
<td>Preterm: unknown</td>
</tr>
<tr>
<td>(l)</td>
<td>Unclassified</td>
</tr>
<tr>
<td>(m)</td>
<td>&gt;1 aetiology</td>
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20. Probable Timing:

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<tbody>
<tr>
<td>(a)</td>
<td>Antenatal including vascular and genetic</td>
</tr>
<tr>
<td>(b)</td>
<td>Perinatal</td>
</tr>
<tr>
<td>(c)</td>
<td>Preterm including perinatal and neonatal</td>
</tr>
<tr>
<td>(d)</td>
<td>Neonatal and post neonatal excluding preterm</td>
</tr>
<tr>
<td>(e)</td>
<td>Unclassifiable</td>
</tr>
</tbody>
</table>

21. Description of the cause if known:

________________________________________________________________________

________________________________________________________________________

________________________________________________________________________
### Paediatric Data

1. **Type of Cerebral Palsy: (please tick one box only)**
   - (a) Spastic
   - (b) Pure Dyskinetic
   - (c) Dystonic Dyskinesia
   - (d) Choreo-Athetoid Dyskinesia
   - (e) Ataxia

2. **Limb Involvement: (please tick one box only)**
   - (a) Hemiplegia
   - (b) Diplegia
   - (c) Quadriplegia
   - (d) Not applicable

3. **Walking Impairment: (please tick one box only)**
   - (a) None: No significant problems with gait
   - (b) Mild: gait functional but non-fluent
   - (c) Moderate: gait obviously abnormal
   - (d) Severe: No independent walking

4. **Visual Impairment: (please tick one box only)**
   - (a) None: 6/12 and better
   - (b) Moderate: 6/18 – 6/60
   - (c) Severe: <6/60
   - (d) Blind: No vision

5. **Hearing Impairment: (please tick one box only)**
   - (a) None: <40 dB loss
   - (b) Moderate: 41-70 dB loss
   - (c) Severe: >71 dB loss

6. **Intellectual Impairment: (please tick one box only)**
   - (a) Profound: IQ < 35
   - (b) Severe: IQ 35-49
   - (c) Moderate: IQ 50-69
   - (d) Mild: IQ 70-84
   - (e) None: IQ >= 85
   - (f) Unknown

7. **Seizures: (please tick one box only)**
   - (a) Never
   - (b) Within first 24 hours only
   - (c) Seizure Free Now
   - (d) Still Active

8. **Feeding Difficulties: (please tick one box only)**
   - (a) None: no apparent problems
   - (b) Mild: some difficulty but feeds self
   - (c) Moderate: unable to feed self with one hand
   - (d) Severe: unable to feed self with either hand

---

Oct 2010
Operational Definitions: Maternal Data

Woman’s study number: maternity chart number
Gravida: Number of times a woman has been pregnant irrespective of outcome (Henderson & Macdonald, 2004).

Parity: The number of times a woman has given birth to a baby over 24 weeks gestation. A woman who has given birth a particular number of times is referred to as para 1, para 2, etc (Henderson & Macdonald, 2004).

Maternal socio-economic group: A system of social stratification based on occupation, income or education. Traditionally the father’s occupation is used as a measure of socio-economic status. The father’s occupation is coded and grouped following the Central statistics Office system of socio-economic groups (ESRI, 2008).

Agreed EDD: Estimated date of delivery as confirmed by ultrasound scan at least 20 weeks gestation. If performed in the first trimester the scan may under or over estimate by 5 days. If performed in the 2nd trimester the scan may under or over estimate by 10 days. If scan results unavailable then calculate by adding 8 calendar months and 7 days to the first day of the last menstrual period. The scan dates are preferred if the menstrual dates are uncertain or there is a discrepancy of more than 14 days (Bailliere’s Dictionary, 2008; Henderson & Macdonald, 2004).

Antenatal Care: Care provided to women and babies during pregnancy to ensure that fetal and maternal health are satisfactory, to enable early detection and treatment of any deviations from normal. This care is provided in Ireland by midwives, GP’s and obstetricians (Henderson & Macdonald, 2004).

Infertility Treatment: Treatment provided to women who are experiencing inability to conceive after 1 year of actively trying (Henderson & Macdonald, 2004).

History of Maternal Disease: Studies have shown that certain maternal illnesses are associated with cerebral palsy (Strijbis et al, 2005; Wu et al, 2006).

Maternal Diabetes:
Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The classification used is by the WHO Expert Committee on the diagnosis and classification of diabetes mellitus (2000). And the NICE guideline on diabetes in pregnancy (2008)

Pre-gestational Type 1: insulin-dependent diabetes due to an absolute deficiency of insulin secretion.

Pre-gestational Type 2: non-insulin-dependent diabetes due to a combination of resistance to insulin action and an inadequate compensatory insulin secretory response. At least initially, and often throughout their lifetime, these individuals do not need insulin treatment to survive.

Gestational diabetes: GDM is defined as any degree of glucose intolerance with onset or first recognition during pregnancy. The definition applies regardless of whether insulin or only diet modification is used for treatment or whether the condition persists after pregnancy. A fasting plasma glucose level of 126 mg/dl (7.0 mmol/l) or casual plasma glucose of 200 mg/dl (11.1 mmol/l) meets the threshold for the diagnosis of diabetes.

Gestational Impaired Glucose Tolerance (IGT): plasma glucose levels during an oral glucose tolerance test are above normal but below those defined as diabetes. The term IGT refers to a metabolic stage intermediate between normal glucose homeostasis and diabetes. This stage includes individuals who have IGT and individuals with fasting glucose levels >110 mg/dl (6.1 mmol/l) but <126 mg/dl (7.0 mmol/l).


Pre-gestation Hypertension: refers to a known history of hypertension pre-pregnancy or an elevated BP > 140/90 mm Hg before 20 weeks gestation.

Pregnancy Induced Hypertension: Hypertension occurring in the second half of pregnancy in a previously normotensive woman, without significant proteinuria or other features of pre-eclampsia.

Pre-eclampsia: A disorder specific to pregnancy usually occurring after 20 weeks gestation. It is usually of rapid onset and characterised by raised blood pressure and excess protein in the urine. Headache, puffiness of the tissues and visual disturbance may be present in some cases. Pre-eclampsia is diagnosed when the blood pressure is >140 mm Hg systolic, or >90 mm Hg diastolic recorded on at least two occasions at least four hours apart with the patient at rest. Proteinuria >0.3 g in twenty-four hours (James & Nelson-Piercy, 2004).
Bleeding after 20 weeks gestation: can be due to a number of causes among them,
Blood Dyscrasias <1%.
Local causes e.g. vulval or cervical infections, trauma or tumours 5%
Ruptured Vasa Praevia <1%
Cause unknown 30%
Placenta Praevia 30%. Bleeding from a placenta that is implanted entirely or partly in the lower uterine segment
Placental abruption 35%. is the detachment of part or the entire placenta from its implantation site after 20 weeks of
pregnancy and before the birth of the baby. Placental abruption may occur as a partial or complete separation and the
associated haemorrhage may be either concealed or apparent. Abruption may be classified as grade 1, 2 or 3 or may be
classified as mild, moderate or severe (Henderson & Macdonald, 2004).

Antenatal Infection: includes urinary tract infection or pyelonephritis confirmed on MSU; temperature >38.5°C for > 24

Pyrexia in labour: maternal temperature >38 degrees Celsius on two or more separate occasions during labour as per
Jacobson et al, 2002. Maternal pyrexia in labour is strongly and independently associated with neonatal encephalopathy
(Impey et al, 2001).

Labour Onset: may be spontaneous with no intervention
   May have labour artificially induced
   May have caesarean section without being in labour

Labour induction: refers to the artificial initiation of labour when the benefits to the mother or the foetus outweigh those
of continuing the pregnancy (NICE, 2008). Prostaglandin induction refers to the insertion of prescribed prostaglandin
compounds into the posterior fornix of the vagina to bring about cervical effacement, dilation and ripening and to
contribute to the contractility of the uterus. Vaginal prostaglandin E2 (PGE2) is the method of induction of labour
generally used once the cervix has been deemed suitable by the Bishop Score.
Artificial Rupture of Membranes (ARM), also known as amniotomy, is the process whereby the membranes are
deliberately ruptured by a midwife or obstetrician during a vaginal examination using an amniotek. ARM can be used to
induce labour when the condition of the cervix is favourable or to augment labour if progress begins to slow.
Synctocinon: a proprietary preparation of synthetic oxytocin that stimulates contraction of uterine muscles.
Augmentation is the process of accelerating progress after labour has begun (Henderson & Macdonald, 2004).

Mode of Birth:
Ventouse Instrumental: may also be documented as a vacuum delivery. The types of ventouse equipment used are the
levi for mid-cavity deliveries and the piston for outlet deliveries.
Forceps Instrumental: There are 3 main types of forceps delivery; Low cavity outlet forceps- Wrigleys, Mid cavity for

Birth positions: both breech presentation and occipitoposterior positions have been linked to increased risk of cerebral
palsy (Badawi et al, 1998b)

Acute intrapartum events associated with risk of CP as defined by the American College of Obstetricians and
Gynaecologists (2003) are: umbilical cord prolapse, shoulder dystocia, uterine rupture, maternal cardio pulmonary arrest
and pathological CTG.

CTG: Cardiotocograph: continuous electronic monitoring of fetal heart rate as well as uterine contractions. The Royal
College of Obstetricians and Gynaecologists (RCOG, 2007) classification is used to diagnose evidence of non-reassuring
fetal status (Anil Kumarman & Gibb, 2008).
### Fetal Heart Rate Classification

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Variability</th>
<th>Deceleration</th>
<th>Acceleration</th>
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</thead>
<tbody>
<tr>
<td>Reassuring</td>
<td>110–160</td>
<td>&gt; or ≤ 5</td>
<td>None</td>
<td>Present</td>
</tr>
<tr>
<td>Non-Reassuring</td>
<td>100 – 109</td>
<td>161 – 180</td>
<td>&lt; 5 bpm for 40–90 mins</td>
<td>Reduced or absent</td>
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<td></td>
<td>Persistent Early. Variable with &gt; 50% of contractions. Single prolonged decelerations up to 3 mins</td>
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<tr>
<td>Abnormal</td>
<td>&lt; 100</td>
<td>&gt; 180</td>
<td>5 for ≥ 60 mins. Either atypical variable with &gt; 50% contractions, late decelerations or both for ≥ 30 mins. Single prolonged decelerations &gt; 3 mins</td>
<td></td>
</tr>
</tbody>
</table>

**Catagorisation of Fetal Heart Rate Traces:**
- **Normal:** A CTG All Four Features Fall Into the Reassuring Category
- **Suspicious:** A CTG Who’s Features Fall into one of the NON-reassuring categories and the remainder of the features are reassuring.
- **Pathological:** A CTG whose features fall into two or more non-reassuring categories or one or more abnormal categories.

**Meconium Stained Liquor:** meconium staining of the amniotic fluid giving it a greenish/brown discolouration (Henderson & Macdonald, 2004).

**Duration of Rupture of Membranes:**
- PROM: Prolonged Rupture of Membranes when there is greater than 24 hours time interval between rupture of membranes and birth. Data collection refers to the time period 1990-1999 and 24 hours was the duration used in the definition at that time (18 hours today).
- PPROM: Preterm Premature Rupture of Membranes is when membrane rupture occurs prior to 37 completed weeks of gestation (Henderson & Macdonald, 2004).

**Placenta:** A membranous vascular organ linking the mother and fetus that develops during pregnancy. The placenta is examined after each birth to ensure normality and completeness. Placental abnormalities have been strongly associated with perinatal stroke or subsequent periventricular leukomalacia or both (Strijbis et al, 2000; Wu & Colford, 2000).

**Histology:** visualisation of the minute structure, composition and function of tissues and organs. A number of placental pathological findings have been described in children who subsequently developed cerebral palsy. Among those are, villous edema, chronic villitis, haemorrhagic endovascularis and thrombosis (Strijbis et al, 2000; Yoon et al, 2003).

### Operational Definitions: Neonatal Data

**DOB, Time of Birth, Sex, Gestation, birth weight and plurality:** basic demographic data recorded in baby notes.

**Apgar Score:** Numerical code applied to the newborns overall general condition.

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<th>1</th>
<th>2</th>
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</thead>
<tbody>
<tr>
<td>Heart rate</td>
<td>None</td>
<td>&lt;100</td>
</tr>
<tr>
<td>Respirations</td>
<td>None</td>
<td>Slow, irregular, gasping</td>
</tr>
<tr>
<td>Muscle tone</td>
<td>Limp</td>
<td>Some flexion</td>
</tr>
<tr>
<td>Reflex irritability</td>
<td>No response</td>
<td>Grimace, Cry</td>
</tr>
<tr>
<td>Colour</td>
<td>White</td>
<td>Body pink, limbs blue</td>
</tr>
</tbody>
</table>

**Resuscitation:** refers to restoration from a state of collapse, as manifest by the Apgar Score. Resuscitation techniques are applied according to the American Academy of Paediatrics (2006) Neonatal Resuscitation Programme (NRP) in which all medical, nursing and midwifery staff attending births in Ireland are trained (Stephenson et al, 2000).

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Cord Blood: refers to taking a blood sample for analysis from the umbilical cord vessels (Stephenson et al, 2000).

Tight Nuchal Cord: refers to an umbilical cord wrapped tightly around the neck of the infant during birth (Henderson & Macdonald, 2004).

Congenital anomaly: malformation present at birth (Stephenson et al, 2000).

Blood gas analysis: refers to taking a blood sample for analysis from an infant's artery, vein or capillary (Korst et al, 1999).

Neonatal illness: a group of neonatal events described in the literature as being associated with cerebral palsy (Murphy, Hope & Johnson, 1997; Walstab et al, 2004).

Neonatal sepsis: presence of a positive blood culture within 72 hours of birth.

Hypotension: mean BP below gestational age on at least 2 successive occasions

Hypoglycaemia: abnormally low blood glucose in the newborn baby. Associated with birth asphyxia.

Pneumothorax: diagnosis confirmed by chest X-ray, requiring insertion of a chest drain.

PDA (patent ductus arteriosus): clinical diagnosis supported by cardiac echo, requiring medication (indomethacin, bronfen) or surgical ligation.

Prolonged ventilation: requiring mechanical ventilation for 7 days and more


Blood transfusion: for either anaemia or hypotension.

Chronic Lung Disease: preterm and still requiring oxygen at 28 days of life

NEC: necrotising enterocolitis, an inflammatory infective condition of the bowel.

Meconium aspiration: Aspiration of meconium confirmed by chest X-ray

Jaundice: severe enough to require treatment with exchange transfusion.

Thrombocytopenia/coagulopathy: abnormality of platelets and clotting factors on blood counts.

Encephalopathy: a clinically defined syndrome of disturbed neurological function in the earliest days of life in the term infant or near-term infant, manifested by difficulty with initiating and maintaining respiration, depression of tone and reflexes, subnormal level of consciousness, and often by seizures. The severity of encephalopathy is graded according to the Sarnat and Sarnat criteria (1979) and Fenichel (1983) (Hankins, 2003; Volpe, 2008).

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>Mild</th>
<th>Grade I</th>
<th>Moderate-Grade II</th>
<th>Severe: Grade III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consciousness</td>
<td>Hyperalert</td>
<td>Lethargic</td>
<td>Stupor/ comatose</td>
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<tr>
<td>Muscle tone</td>
<td>Normal/hypertonia</td>
<td>Mild hypotonia</td>
<td>Flaccid</td>
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<tr>
<td>Seizures</td>
<td>None</td>
<td>Common</td>
<td>Difficult to manage</td>
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<tr>
<td>Intracranial pressure</td>
<td>Normal</td>
<td>Normal</td>
<td>Elevated</td>
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<tr>
<td>Suck Reflex</td>
<td>Weak</td>
<td>Weak or Absent</td>
<td>Absent</td>
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<tr>
<td>Moro Reflex</td>
<td>Strong</td>
<td>Weak</td>
<td>Absent</td>
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<tr>
<td>Respirations</td>
<td>Normal-shallow</td>
<td>Poor respiratory effort</td>
<td>Ventilated</td>
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<tr>
<td>Heart rate</td>
<td>Tachycardia</td>
<td>Bradycardia</td>
<td>Variable</td>
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<tr>
<td>EEG Findings</td>
<td>Normal</td>
<td>Periodic or paroxymal</td>
<td>Periodic or isoelectric</td>
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<tr>
<td>Duration</td>
<td>&lt;24 hrs</td>
<td></td>
<td>weeks</td>
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</table>

Multisystem failure within 72 hours: In response to hypoxia, blood flow to the brain and other vital organs (heart, adrenals, placenta) are maintained at the expense of blood flow to the kidneys, liver, gut and lungs. The occurrence of dysfunction of at least one of the organ systems in conjunction with encephalopathy provides an indication of the severity of the asphyxia insult and criteria for the prediction of the long term outcome (Low, 1997; Korst et al, 1999). For all the systems, dysfunction was evaluated over the first week of life.

Cerebral Radiology: refers to investigative scanning of the cerebral hemispheres to detect any abnormalities. Grading of IVH is according to Papile (1978) classification (Trewitt et al, 1992; Stephenson et al, 2000).

Cerebral Radiology Results: the findings of ultrasound, CT and MRI scanning were classified based on official reports from the neuroradiologists.

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Known cause of CP: For some children affected by cerebral palsy there is a clear identifiable cause in the antenatal, intrapartum, neonatal or post neonatal period (Cans et al, 2004). The aetiological classification used was based on given clinical information combined with available neuro-imaging information and documented expert opinion by neurologists involved in the children's care.

Probable Timing: The probable timing classification used was based on given clinical information combined with available neuro-imaging information and documented expert opinion by neurologists involved in the children's care.

Operational Definitions: Paediatric Data

The data related to the subsequent diagnosis and classification of cerebral palsy is based on the Surveillance of the Cerebral Palsy in Europe (SCPE, 2000) system which is the system used for registration of children on the West of Ireland Cerebral Palsy Register (WCPR). Once a child has been identified as having cerebral palsy they are assessed by a trained paediatrician and diagnosed and classified according to this set criteria. This data is then notified to the manager of the WMCR and entered on the register.

Type of cerebral palsy: based on the SCPE decision tree for subtype of cerebral palsy.

Limb Involvement:
Hemiplegia: limbs affected on one side of the body only
Diplegia: limbs affected on both sides of the body
Quadriplegia: both upper and lower limbs affected

Walking Impairment:
None: No significant problem with gait, walks fluently
Mild: Gait functional but non-fluent
Moderate: Gait obviously abnormal reducing mobility
Severe: No independent walking

Visual Impairment:
None: Normal or near normal vision = 6/12 and better
Moderate: Moderately impaired vision = 6/18-6/60
Severe: Severely impaired vision = <6/60
Blind: No vision

Hearing Impairment:
None: Normal or near normal hearing with <40dB loss
Moderate: Moderately impaired hearing with 41-70dB loss
Severe: Severely impaired hearing with >71dB loss

Intellectual ability, based on a measurement of intelligence quotient (IQ), is assessed by psychologists and classified using the Diagnostic and Statistical Manual of Mental Disorders, 4th edition.

Seizures:
Within the first 24 hours: any seizure activity noted in first 24 hours of life
24 hours – 28 days: any seizure activity noted from 24 hours of life to 28 days of age.
Seizure Free: has had childhood seizures but hasn’t suffered a seizure in the preceding two years.
Still Active: continues to have seizures and/or is on medication to control seizures.

Feeding Difficulties:
None: No apparent problems
Mild: Some difficulty but able to feed self
Moderate: unable to feed self with one hand
Severe: unable to feed self with either hand

Oct 2010
References


NICE (2008) Induction of Labour: NICE clinical guideline 70. Online @ www.nice.org.uk


Oct 2010


Appendix 3.8:
Content validity Evaluation
Content validity Evaluation

I would be very grateful if you would participate in this expert evaluation of the Data Extraction Tool that I propose to use for my epidemiological study into cerebral palsy.

The Data Extraction Tool is divided into three sections; one collecting maternal data, one collecting neonatal data and another collecting paediatric data relating to the type and severity of cerebral palsy. Each data item is defined in the operational definitions section of the form and is fully referenced in the reference list.

Using the following content validity evaluation form, I would appreciate if you would:

- Rate the relevance of each item in the data extraction tool on a scale of 1-4 using the following criteria,
  
  1 = Not relevant
  2 = Unable to assess relevance without revision
  3 = Relevant but needs minor alteration
  4 = Very relevant

- Provide suggestions regarding any modifications you feel are necessary to any of the questions.
- Identify any necessary questions you feel I have omitted.
- Identify any existing questions you feel should be omitted.
### Maternal Data

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<td>Bleeding after 20 weeks</td>
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<td>Antenatal Infection</td>
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<td>Pyrexia in labour</td>
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<td>Mode of birth</td>
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<td>Labour CTG</td>
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<td>Meconium Stained Liquor</td>
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<td>Duration of Rupture of Membranes</td>
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<td>Gestation at Rupture of membranes</td>
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<td>9 Plurality</td>
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<td>10 Apgar Score</td>
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<td>12 Cord blood</td>
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<td>13 Tight Nuchal Cord</td>
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<td>19 Evidence of multisytem failure</td>
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<td>20 Cerebral radiology</td>
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Any Comments or Suggestions regarding specific sections of the form:

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Any overall comments or suggestions:

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Thank you very much for your time and expertise in this evaluation process. It is greatly appreciated.
Appendix 3.9: Mothers Letter of Consent
INFORMATION SHEET FOR POTENTIAL PARTICIPANTS
(For mothers of children under 18 years old with cerebral palsy)

1. Title of the study: Cerebral palsy in the West of Ireland and the application of the international criteria for the identification of acute intrapartum hypoxia: a cohort study.

2. Introduction: I am a children’s nurse and midwife currently studying for a higher degree (PhD) at the National University of Ireland, Galway. I am writing to invite you to participate in a research study being undertaken as part requirement for my studies. The following information sheet will help you to understand why the research is being done and what it would involve for you. Please take time to read this carefully before you decide whether or not I can include you in the study. This request has been sent to 100 children in the West of Ireland with cerebral palsy.

3. What the study involves: You do not have to actually do anything for this study except give me permission to look at your medical records. The aim of this study is to examine information about the occurrence of certain factors during pregnancy, birth and the newborn period thought to be associated with cerebral palsy. I have a list of information that I would like to get from maternity charts and paediatric charts. The type of information I am interested in are things like: how long was the pregnancy, were you ill during the pregnancy, what weight was the baby, what condition was the baby in at birth, was the baby admitted to the neonatal unit, what type of cerebral palsy does the child have now? I will then examine the information to see how all the different factors link together. I would like you to consider participating in my study examining this information about cerebral palsy. As this is your private information I am writing to ask for your permission before I can look at your records.

4. Confidentiality: Your identity and that of your child will remain confidential. I will put a number rather than your name on the information I get from the records so that you cannot be identified. The information I get will be stored on a password protected computer in a locked office. The anonymous information will not be seen by anybody other than me, my research supervisors in the university and possibly a statistician if I need assistance with data analysis. No individuals will be identified in any documentation, publications or presentations about the study.

5. Storage of information: All documents associated with this study will be stored in a password protected computer located in a locked office. The signed Consent Forms will be stored securely in a locked cabinet with access strictly restricted to personnel working on the study. The information will be kept for 5 years in keeping with the Data Protection (Amendment) Act (2003).

Anyone less than 18 years old is a minor/child. In all cases permission to invite children under 18 to participate in research must be sought from parents or guardians (Law Reform Commission, 2005).
6. Possible benefits: There is no benefit to you directly. However, this study will provide valuable information essential to our understanding of cerebral palsy and may generate knowledge that will provide greater understanding of this complex condition. The findings may be useful to make recommendations for ongoing management of cerebral palsy and the services provided. The information generated will also allow us to compare cerebral palsy in the West of Ireland with cerebral palsy elsewhere.

7. Risks: There are no foreseeable risks to you by being involved in this study. No individuals will be identified in any documentation, publications or presentations about the study.

8. Voluntary participation: Participation in this study is voluntary. It is up to you to decide if you would like to take part and if you agree to your child taking part. If you do decide to take part you will be asked to sign a consent form on behalf of both yourself and your child who is under 18 years old. As you are most familiar with your own child, you can decide the level of involvement of your child in the decision regarding participation. If you decide not to take part or withdraw from the study this will not affect the services you or your child receives now or in the future. Participating in the study means that you consent for your medical records and your child’s medical records to be looked at by me. Participation does not involve any interview or any other type of examination.

9. Permission: This study has received research ethical approval from the HSE and Galway University Ethics Committees. The function of the ethics committee is to ensure that I protect the safety, rights, wellbeing and dignity of anybody who participates in the study. I have also received permission from your paediatrician to approach you.

10. The Results: The research will continue until January 2012. I will then circulate the results among the paediatricians and the local services you have contact with so that you have access to the results.

11. Further Information: I will be happy to answer any questions you may have or clarify any details you require regarding the study. My contact details are below and please feel free to contact me if anything is not clear or if you require any more information. If you have any concerns about this study and wish to contact someone independent and in confidence, you may contact the Chairperson of the National University of Ireland, Galway, Research Ethics Committee at ethics@nuigalway.ie.

12. Signatures required: There is one consent form enclosed. It requires you to sign twice. The first signature is for mothers permitting me to access their maternity records. The second signature is for mothers permitting me to access their child’s records. I need to look at both mother and child records to form a complete picture.

Anyone less than 18 years old is a minor/child. In all cases permission to invite children under 18 to participate in research must be sought from parents or guardians (Law Reform Commission, 2005).
If you do decide to participate in this study I would be grateful if you could take the time to sign the enclosed consent form and return it to me in the enclosed stamped addressed envelope as soon as possible. I need **two signatures** please; one allowing me to access your records and one allowing me to access your child’s records. I would like to get the consent forms back within 2 weeks so that I can commence collecting the information for the study.

I am very aware of the many demands that are placed on you and consequently I appreciate very much your taking the time to read this information sheet.

__________________________
Patricia Healy,
PhD (Midwifery) Student
PhD Room 234, 1st Floor Aras Moyola
School of Nursing and Midwifery
National University of Ireland, Galway
University Road
Galway

Telephone No: 089 4343711
Email: p.healy5@nuigalway.ie

Anyone less than 18 years old is a minor/child. In all cases permission to invite children under 18 to participate in research must be sought from parents or guardians (Law Reform Commission, 2005).
Consent Form for Participation in the Study
(Regarding children with cerebral palsy who are under 18 years old)

Title of the Study: Cerebral palsy in the West of Ireland and the application of the international criteria for the identification of acute intrapartum hypoxia: a cohort study.

Name of Researcher: Patricia Healy (Nurse/ Midwife/ PhD Student)

Researchers Contact Details: Telephone 089 4343711
Email: p.healy5@nuigalway.ie

Declaration:
1. I confirm that I have read and understand the information sheet for the above study and have had the opportunity to ask questions. I understand what is being proposed and the procedures involved have been explained to me.

2. Having given this consent, I understand that I have the right to withdraw myself or my child from the study at any time without disadvantage to myself or my child and without being obliged to give any reason.

3. I understand that the involvement of me and my child in this study will remain strictly confidential. I understand that all information collected in this study will be treated as confidential and that my identity and my child’s identity will remain confidential. Only the researchers involved in the study will have access to the data.

4. I hereby fully and freely consent to my participation and my child’s participation in the study that has been fully explained to me.

5. I agree that the researcher, Patricia Healy, can access my records and my child’s records to obtain the information required for the study.

Please sign below.

Mothers signature permitting access to mother’s records.

Date

Mothers signature permitting access to child’s records (for children under 18 years).

Date

Anyone less than 18 years old is a minor/child. In all cases permission to invite children under 18 to participate in research must be sought from parents or guardians (Law Reform Commission, 2005).
Appendix 3.10:
Children’s Letter of Consent
INFORMATION SHEET FOR POTENTIAL PARTICIPANTS
(For young adults with cerebral palsy who are now over 18 years old and their mothers)

1. Title of the study: Cerebral palsy in the West of Ireland and the application of the international criteria for the identification of acute intrapartum hypoxia: a cohort study.

2. Introduction: I am a children’s nurse and midwife currently studying for a higher degree (PhD) at the National University of Ireland, Galway. I am writing to invite you to participate in a research study about cerebral palsy being undertaken as part requirement for my studies. The following information sheet will help you to understand why the research is being done and what it would involve for you. Please take time to read this before you decide whether or not I can include you in the study. This request has been sent to 100 children in the West of Ireland with cerebral palsy.

3. What the study involves: You do not have to actually do anything for this study except give me permission to look at your medical records. The aim of this study is to examine information about the occurrence of certain factors during pregnancy, birth and the newborn period thought to be associated with cerebral palsy. I have a list of information that I would like to get from maternity charts and paediatric charts. The type of information I am interested in are things like: how long was the pregnancy, were you ill during the pregnancy, what weight was the baby, what condition was the baby in at birth, was the baby admitted to the neonatal unit, what type of cerebral palsy does the child have now? I will then examine the information to see how all the different factors link together. I would like you to consider participating in my study examining this information about cerebral palsy. As this is your private information I am writing to ask for your permission before I can look at your records.

4. Confidentiality: Your identity will remain confidential. I will put a number rather than your name on the information I get from your records so that you cannot be identified. The information I get will be stored on a password protected computer in a locked office. The anonymous information will not be seen by anybody other than me, my research supervisors in the university and possibly a statistician if I need assistance with data analysis. No individuals will be identified in any documentation, publications or presentations about the study.

5. Storage of information: All documents associated with this study will be stored in a password protected computer located in a locked office. The signed Consent Forms will be stored securely in a locked cabinet with access strictly restricted to personnel working on the study. The

Anyone over 18 years old is legally an adult. Respect for autonomy considers the individual as an independent person who is able to make choices for him/herself. The Data Protection (Amendment) Act (2003) holds that where the data subject by reasons of his or her physical or mental incapacity or age, is or is likely to be unable to appreciate the nature and effect of such consent, it may be given by a parent or guardian as proxy consent.
information will be kept for 5 years in keeping with the Data Protection (Amendment) Act (2003).

6. Possible benefits: There is no benefit to you directly. However, this study will provide valuable information essential to our understanding of cerebral palsy and may generate knowledge that may provide greater understanding of this very complex condition. The findings may be useful to make recommendations for ongoing management of cerebral palsy and the services provided. The information generated will also allow us to compare cerebral palsy in the West of Ireland with cerebral palsy elsewhere.

7. Risks: There are no foreseeable risks to you by being involved in this study. No individuals will be identified in any documentation, publications or presentations about the study.

8. Voluntary participation: Participation in this study is voluntary. It is up to you to decide if you would like to take part. If you do decide to take part you will be asked to sign a consent form. If you decide not to take part or withdraw from the study this will not affect the services you receive now or in the future. Participating in the study means that you (mother and young person) consent for your medical records to be looked at by me. Participation does not involve any interview or any other type of examination.

9. Permission: This study has received research ethical approval from the HSE and Galway University Ethics Committees. The function of the ethics committee is to ensure that I protect the safety, rights, wellbeing and dignity of anybody who participates in the study. I have also received permission from your paediatrician to approach you.

10. The Results: The research will continue until January 2012. I will then circulate the results among the paediatricians and the local services you have contact with so that you have access to the results.

11. Further Information: I will be happy to answer any questions you may have or clarify any details you require regarding the study. My contact details are below and please feel free to contact me if anything is not clear or if you require any more information. If you have any concerns about this study and wish to contact someone independent and in confidence, you may contact the Chairperson of the National University of Ireland, Galway, Research Ethics Committee at ethics@nuigalway.ie.

12. Signatures required: There are two consent forms enclosed. There is one for mothers permitting me to access their records. There is another for young adults with cerebral palsy, over the age of 18 years, permitting me to access their records. If, for any reason, the young adult is 18 years old or is unable to understand and/or cannot sign, then the mother may sign on their behalf. The Data Protection (Amendment) Act (2003) holds that where the data subject by reason of his or her physical or mental incapacity or age, is or is likely to be unable to appreciate the nature and effect of such consent, it may be given by a parent or guardian as proxy consent.
unable to sign their own consent form, there is an option for their mother to sign on their behalf (proxy consent). The proxy consent should only be used after the young adult has decided, in conjunction with their parent that they agree for someone to sign on their behalf.

If you do decide to participate in this study I would be grateful if you could take the time to sign the enclosed 2 consent forms giving me permission to access records of the mother and records of the young person with cerebral palsy and return it to me in the enclosed stamped addressed envelope as soon as possible. I would like to get the consent forms back within 2 weeks so that I can commence collecting the information for the study.

I am very aware of the many demands that are placed on you and consequently I appreciate very much your taking the time to read this information sheet.

Patricia Healy,
PhD (Midwifery) Student
PhD Room 234, 1st Floor Aras Moyola
School of Nursing and Midwifery
National University of Ireland, Galway
University Road
Galway

Telephone No: 089 4343711
Email: p.healy@nuigalway.ie

Anyone over 18 years old is legally an adult. Respect for autonomy considers the individual as an independent person who is able to make choices for him/herself. The Data Protection (Amendment) Act (2003) holds that where the data subject by reasons of his or her physical or mental incapacity or age, is or is likely to be unable to appreciate the nature and effect of such consent, it may be given by a parent or guardian as proxy consent.
Mothers Consent Form for Participation in the Study
(For mothers of children with cerebral palsy who are now over 18 years old)

Title of the Study: Cerebral palsy in the West of Ireland and the application of the international criteria for the identification of acute intrapartum hypoxia: a cohort study

Name of Researcher: Patricia Healy (Nurse/ Midwife/ PhD Student)

Researchers Contact Details: Telephone 089 4343711
Email: p.healy5@nuigalway.ie

Declaration:
1. I confirm that I have read and understand the information sheet for the above study and have had the opportunity to ask questions. I understand what is being proposed and the procedures involved have been explained to me.

2. Having given this consent I understand that I have the right to withdraw from the study at any time without disadvantage to myself and without being obliged to give any reason.

3. I understand that my involvement in this study will remain strictly confidential. I understand that all information collected in this study will be treated as confidential and that my identity will remain confidential. Only the researchers involved in the study will have access to the data.

4. I hereby fully and freely consent to participate in the study that has been fully explained to me.

5. I agree that the researcher, Patricia Healy, can access my records to obtain the information required for the study.

Please sign below.

Mothers signature permitting access to mother’s records. ___________________________ Date: ___________________________

Anyone over 18 years old is legally an adult. Respect for autonomy considers the individual as an independent person who is able to make choices for him/herself. The Data Protection (Amendment) Act (2003) holds that where the data subject by reasons of his or her physical or mental incapacity or age, is or is likely to be unable to appreciate the nature and effect of such consent, it may be given by a parent or guardian as proxy consent.
Young Adults Consent Form for Participation in the Study
(For children with cerebral palsy who are now over 18 years old)

Title of the Study: Cerebral palsy in the West of Ireland and the application of the international criteria for the identification of acute intrapartum hypoxia: a cohort study

Name of Researcher: Patricia Healy (Nurse/ Midwife/ PhD Student)

Researchers Contact Details: Telephone 089 4343711
Email: p.healy5@nuigalway.ie

Declaration:
1. I confirm that I have read and understand the information sheet for the above study and have had the opportunity to ask questions. I understand what is being proposed and the procedures involved have been explained to me.

2. Having given this consent I understand that I have the right to withdraw from the study at any time without disadvantage to myself and without being obliged to give any reason.

3. I understand that my involvement in this study will remain strictly confidential. I understand that all information collected in this study will be treated as confidential and that my identity will remain confidential. Only the researchers involved in the study will have access to the data.

4. I hereby fully and freely consent to participate in the study that has been fully explained to me.

5. I agree that the researcher, Patricia Healy, can access my records to obtain the information required for the study.

Please sign below.

Young adult’s signature permitting access to their records. Date

Mothers signature permitting access (by proxy if needed) to child’s records. Date

Anyone over 18 years old is legally an adult. Respect for autonomy considers the individual as an independent person who is able to make choices for him/herself. The Data Protection (Amendment) Act (2003) holds that where the data subject by reasons of his or her physical or mental incapacity or age, is or is likely to be unable to appreciate the nature and effect of such consent, it may be given by a parent or guardian as proxy consent.