Defining Features And Aetiology Of Hypoxic-Ischaemic Encephalopathy

Thesis submitted for the degree of Doctor of Medicine (MD)

By

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June 2018

Abstract

Defining Features and Aetiology of Hypoxic-Ischaemic Encephalopathy. Dr Pooja Devi Harijan

This thesis seeks to set out the background, methods, results and discussion and conclusion of an observational study of the defining features and aetiology of moderate-severe hypoxic-ischaemic encephalopathy (HIE).

Firstly, the epidemiology, pathophysiology and treatment of HIE are outlined. A number of existing epidemiological definitions are described, compared and contrasted. The difficulties of defining HIE clearly and consistently for epidemiological purposes are discussed. The role of intrapartum hypoxia and other aetiological factors in HIE is introduced. The challenges of exploring the aetiology of HIE are discussed. The consideration of potential methodologies to study this topic is described.

The aims and objectives of the study are presented. The design of the study and study components are each then described in turn. These include the pilot study, retrospective cohort study, development of a reference standard by expert consensus, observational study of possible aetiological factors, and measurement of validity of epidemiological definitions are each described in turn.

The results of the study are described in turn. 168 infants with symptoms of neonatal encephalopathy were identified and notes were obtained for 153 of these infants. The observed maternal, neonatal and paediatric features of these infants and the development of a reference standard by expert consensus are described. The application of the reference standard to the study population leading to the identification of 54 infants with neonatal encephalopathy (NE) of whom 29 (53.7%) infants had moderate-severe HIE, is described. The prevalence of possible aetiological factors in infants with NE and the HIE and non-HIE subgroups are described.

Finally, the study findings, strengths and limitations are discussed. The defining features of HIE and the prevalence of risk factors in this population compared to similar studies where available, are presented. The implications of these findings for future clinical practice and research are discussed.

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List of abbreviations

aEEG	amplitude-integrated electroencephalogram
BA	birth asphyxia
BW	birth weight
CFM	cerebral function monitoring
CP	cerebral palsy
CTG	cardiotocogram
DWMRI	diffusion weighted magnetic resonance imaging
EEG	electroencephalogram
FBC	full blood count
FHR	fetal heart rate
GA	gestational age
HIE	hypoxic-ischaemic encephalopathy
ICD	International Classification of Diseases
IUGR	intra-uterine growth retardation
LBW	low birth weight
ELBW	extremely low birth weight
MRI	magnetic resonance imaging
MRS	magnetic resonance spectroscopy
NE	neonatal encephalopathy
NNAP	National Neonatal Audit Project
OFC	Occipito-frontal Circumference
SGA	Small for Gestational Age
TH	Therapeutic Hypothermia
TNS	The Neonatal Survey
ToBy trial	Total Body Hypothermia trial
USS	Ultrasound scan

Chapter 1: Introduction

1.1 Background

Hypoxic-ischaemic encephalopathy (HIE) is a leading cause of childhood death and disability. Globally it has been estimated to cause 1.2 million infant deaths per year and to lead to cerebral palsy, epilepsy or developmental delay in a further 1.2 million infants per year[1,2]. HIE consists of disordered brain function (encephalopathy) in association with lack of or reduced blood supply and consequently reduced supply of oxygen (hypoxia-ischaemia) to the brain.

The epidemiological definition of HIE is important in identifying appropriate cases in public health surveillance. Diagnostic complexities include the lack of valid markers of hypoxia-ischaemia and the poorly defined aetiology. For over twenty years challenges in clarity and consistency of epidemiological definitions used in the surveillance of HIE have been identified[3,4,5,6,7,8]. Many efforts have been made to narrow the nomenclature used to describe HIE and create a standard definition.

HIE has historically been described as a birth complication, with the assumption being that the hypoxia-ischaemia occurs due to an identifiable and/or preventable event during birth. In cases where this assumption has been supported by the legal process there have been cerebral palsy claims attributed to obstetric negligence thought to average £1 million each, and to annually account for about half of the estimated £430 million annual cost of litigation in the NHS[9]. This assumption has been challenged over recent years with increasing awareness of gaps in our understanding of the aetiology of HIE.

In this thesis the term HIE is used to refer to moderate to severe neonatal encephalopathy (disordered brain function) present at birth in term infants and caused by hypoxia-ischaemia.

1.1.1 Nomenclature

There has been a long and continuing debate in the academic literature about the terms “neonatal encephalopathy” and “hypoxic-ischaemic encephalopathy”.

A number of authors have advocated use of the term “neonatal encephalopathy” in preference to the term “HIE” [5,6,8,10,11,12,13]. For example, the UK National Perinatal Epidemiology Unit (NPEU) commented that the term “HIE” is unhelpful to both the understanding of aetiology and parental interpretation of the cause of their infant’s condition[5]. Conversely a number of authors have advocated continued use of the term “HIE”[7], arguing that the term neonatal encephalopathy is inadequate to describe those cases of neonatal encephalopathy caused by hypoxia-ischaemia. In line with this, whilst the current WHO International Classification of Diseases[14] (ICD-10) gives classification codes for “intrauterine hypoxia”, “birth asphyxia” and “HIE of newborn”, the next edition (ICD-11) will includes an additional classification code for “neonatal encephalopathy”[15].

1.1.2 Other causes of neonatal encephalopathy

There are many causes of neonatal encephalopathy including metabolic disturbance, intracranial haemorrhage, acute ischaemic stroke, cerebral venous sinus thrombosis, intracranial infection, and drug exposure[7]. These causes may present identically to HIE and it can be difficult to distinguish HIE from NE of other aetiology. HIE may co-exist with NE due to another cause[16]. Indeed, depending on the cause, infants with NE due to another cause may be more susceptible to HIE[16].

1.1.3 Epidemiological studies of HIE

In 2010, 1.15 million babies (uncertainty range:0.89–1.60 million; 8.5 cases per 1,000 live births) were estimated to have developed NE associated with intrapartum events, with 96% born in low and middle income countries, as compared with 1.60 million in 1990 (11.7 cases per 1,000 live births)[17]. The estimated incidence of moderate to severe HIE varies between 1 and 8 per 1000 live births in developed countries to 26 per 1000 live births in developing countries[18]. Incidence studies to date have used several different definitions due to the lack of a universally agreed definition[5,6,8] leading to difficulties in comparability between datasets and identification of trends. There is a striking difference in estimated incidence between low resource countries (such as a recent Tanzanian estimate of 52.2 per 1000 live births[19] and high resource countries (such as a recent Swedish estimate of 1.7 per 1000 live births[20]; part of

this variation may reflect the relatively high prevalence of complicated deliveries in low resource countries. The reported incidence of moderate to severe HIE tends to be higher in preterm than in term infants, with estimates in high resource countries ranging from 1.3/1000 live births to 5–9/1000 live births[21,22,23]; further studies are needed as existing studies are small and few.

1.1.4 Pathophysiology of HIE

The pathophysiology of HIE has been studied using a variety of methods, predominantly animal models[24]. Animal models often consist of exposing the animal fetus to experimental hypoxia, for example by ligating the common carotid artery, and evaluating the response. A number of models have been used beginning with mammals such as piglets, sheep and primate models[25] followed by the Vannucci rat model[26]; while the former have greater similarity to humans, the latter have the advantage of scope for genetic modification to allow study of the role of individual genes.

This approach allows study of the response to hypoxia without exposure to other confounding factors. However the model may not be representative and may involve assumptions which may or may not be true of the human infant with HIE. For example it is not clear whether the sudden complete hypoxia in a previously healthy organism that is induced during this process is representative of the timing or nature of the hypoxia that occurs in HIE or the condition of the infant at the time of exposure[24].

Within these caveats, a number of useful processes in the response of the organism to hypoxia have been identified from animal models. Following disruption of delivery of oxygen to the fetus by experimental hypoxia the physiological “diving” reflex is triggered leading to bradycardia associated with vasoconstriction of some vascular beds and reduction in cardiac output[27]. The healthy fetal brain tries to compensate for this to preserve cerebral blood flow. This process is known as cerebral autoregulation. As blood oxygen levels fall (hypoxia) and/or blood pH falls (acidosis) the effectiveness of cerebral autoregulation decreases. This results in a fall in cerebral blood flow with consequent disruption of oxygen and glucose delivery to the brain[28].

The reduction in oxygen and glucose supply to the brain prevents aerobic metabolism and results in primary energy failure (decreased adenosine triphosphate (ATP) production and increased lactate production)[29]. This primary energy failure causes failure of membrane stabilising processes which initiates excitotoxic cascades (massive depolarisation of neurons; glutamate release; activation of N-methyl-D-aspartate receptor mediated calcium channels and rise in intracellular calcium)[30] leading to cell death predominantly by apoptosis (programmed cell death) as well as by necrosis (pathological cell death). There is then a latent period of 6-48 hours[31] during which cerebral blood flow is re-established. Following this there may be secondary mitochondrial energy failure[31,32]. The mechanism of this is well characterised and is thought to be mediated by oxidative stress, excitotoxicity and inflammation, which may lead to secondary brain injury, with cell death mainly by necrosis[32].

There is some support for these observations in animals from post mortem studies of infants with HIE which have identified neuropathological processes such as oedema, degeneration, and necrosis of nerve cells[32] corresponding to the processes identified in animal studies. Emerging neuroimaging techniques such as diffusion tensor fractional anisotropy[33] and enhanced T2* weighted angiography[34] have also suggested corresponding ultrastructural imaging findings although such techniques are still in their infancy.

There is also indirect evidence to support the animal studies from radiological patterns of injury. The patterns correspond to selective vulnerability to the processes above of different areas of the brain[35,36]. Chronic partial or moderate hypoxia leads to shunting of blood from the anterior to posterior circulation with injury to the cortex and watershed areas of the cerebral hemispheres[35]. Acute near-total hypoxia leads to injury of the deep grey matter (basal ganglia and thalami)[36,37], which are the areas of the brain with the highest metabolic activity[38] as well as the highest concentrations of excitatory amino acid receptors[39,40] are more susceptible to hypoxic ischaemic injury[41].

1.2 Clinical features of HIE

The first case series of HIE was described in 1976 by Sarnat and Sarnat[42] in a case series of 21 infants who had a birth history of acute fetal distress, with a

syndrome characterised by abnormalities of tone, consciousness and seizures as well as abnormal respiration. The condition has since been observed in many large observational studies incorporating infants with and without a birth history of acute fetal distress, leading to more detailed description. The clinical diagnosis of HIE is made when there is a clinical presentation of neonatal encephalopathy which is thought to have arisen due to fetal hypoxia-ischaemia. Neonatal encephalopathy is “a clinically defined syndrome of disturbed neurological function in the earliest days of life in the term infant, manifested by difficulty in initiating and maintaining respiration, depression of tone and reflexes, subnormal level of consciousness and often seizures”[12].

1.2.1 Total body hypothermia study criteria for HIE

The most widely used clinical criteria applied to the definition of moderate to severe HIE in the UK are those developed for use in the total body hypothermia (ToBy) randomised controlled trial of therapeutic hypothermia for HIE[43]. This was a large, non-blinded, randomised controlled clinical trial of 325 infants with moderate-severe HIE. Infants were randomised within 6 hours of birth to either a control group with the rectal temperature kept at 37 +/- 0.2 ^{O}C or to whole body cooling, or to an intervention group subjected to targeted temperature reduction of rectal temperature to 33-34 ^{O}C for 72 hours using a cooling blanket followed by controlled rewarming. It found that infants randomised to whole-body hypothermia for 72 hours had statistically significantly increased rate of survival without neurological abnormality at 18 months of age (relative risk 1.57, 95% CI 1.16-2.12; p=0.003).

Table 1.1: TOBY[43] criteria for HIE

• The infant is assessed sequentially by criteria A and B listed below:
• Infants ≥ 36 completed weeks gestation admitted to the NICU with at least one of the following: o Apgar score of ≤ 5 at 10 minutes after birth o Continued need for resuscitation, including endotracheal or mask ventilation, at 10 minutes after birth o Acidosis within 60 minutes of birth (defined as any occurrence of umbilical cord, arterial or capillary pH < 7.00) o Base Deficit ≥ 16 mmol/L in umbilical cord or any blood sample (arterial, venous or capillary) within 60 minutes of birth • Infants that meet criteria A will be assessed for whether they meet the neurological abnormality entry criteria (B).
• Moderate to severe encephalopathy, consisting of altered state of consciousness (lethargy, stupor or coma) AND at least one of the following: o hypotonia o abnormal reflexes including oculomotor or pupillary abnormalities o absent or weak suck o clinical seizures

The TOBY criteria have high clinical utility as the markers of hypoxia-ischaemia chosen are objective and easy to measure, which is particularly important in the use of the criteria to select patients efficiently for early diagnosis and treatment. However the neurological criteria may be erroneously recorded by inexperienced observers; other criteria, such as those developed for the large randomised controlled trial of therapeutic hypothermia in the United States of America[44], have countered this problem by incorporating mandatory certification of neonatologists in infant neurological examination.

1.2.2 Classification of severity of HIE

1.2.2.1 Sarnat and Sarnat classification

The extent of neurological dysfunction in HIE was initially classified by Sarnat and Sarnat[42] into three stages, stage 1, 2 and 3. The stages reflect the multiple presentations of encephalopathy.

Table 1.2: Sarnat and Sarnat[42] classification system

	Stage 1	Stage 2	Stage 3
Level of consciousness	Hyperalert	Lethargic or obtunded	Stuporous
Neuromuscular control			
Muscle tone	Normal	Mild hypotonia	Flaccid
Posture	Mild distal flexion	Strong distal flexion	Intermittent decerebration
Stretch reflexes	Overactive	Overactive	Decreased or absent
Segmental myoclonus	Present	Present	Absent
Complex reflexes			
Suck	Weak	Weak or absent	Absent
Moro	Strong, low threshold	Weak, incomplete, high threshold	Absent
Oculo vestibular	Normal	Overactive	Weak or absent
Tonic neck	Slight	Strong	Absent
Autonomic function	Generalized sympathetic	Generalized parasympathetic	Both systems depressed
Pupils	Mydriasis	Miosis	Variable, often unequal, poor light reflex
Heart rate	Tachycardia	Bradycardia	Variable
Bronchial and salivary secretions	Sparse	Profuse	Variable
Gastrointestinal motility	Normal or decreased	Increased, diarrhoea	Variable
Seizures	None	Common, focal or multifocal	Uncommon (excluding decerebration)
Electroencephalogram findings	Normal (awake)	Early: low-voltage continuous delta and theta Later: periodic pattern (awake) Seizures: focal 1-to 1-Hz spike-and-wave	Early: periodic pattern with Isopotential phases Later: totally isopotential
Duration	Less than 24 hours	2 – 14 days	Hours to weeks

The construct validity of this description was supported by reproduction of these clinical features in a contemporaneous paper[45]. With time it has become apparent that this staging system has two major limitations for clinical use. Firstly, infants frequently have a combination of abnormalities from more than one stage

category[28]. Secondly, it may be more appropriate to grade rather than to stage HIE as the implied transitivity between the stages is not clinically relevant in the majority of infants[8].

1.2.2.2 Other classifications of severity of HIE

Since its development, the Sarnat classification has been modified to define mild, moderate or severe encephalopathy. There are now a number of classifications of severity, such as the Levene criteria[46] and TOBY[43] severity criteria (Table 1.3) which are more easily applied in the clinical setting.

Table 1.3: Criteria for defining moderate and severe encephalopathy in the TOBY study

Parameter	**Moderate Encephalopathy**	**Severe Encephalopathy**
Level of consciousness	Reduced response to stimulation	Absent response to stimulation
Spontaneous Activity	Decreased Activity	No activity
Posture	Distal flexion, complete extension	Decerebrate
Tone	Hypotonia (focal or general)	Flaccid
Suck	Weak	Absent
Moro	Incomplete	Absent
Pupils	Constricted	Constricted
Heart rate	Bradycardia	Variable
Respiration	Periodic breathing	Apnoea

Moderate and severe HIE have been combined for study in this thesis because they have many clinical and prognostic similarities[47,48].

1.2.3 Clinical markers of fetal hypoxia

There is no single practical and valid marker of fetal hypoxia-ischaemia. However in the absence of a gold standard, in clinical practice a number of markers can be evaluated in infants with encephalopathy in order to assess the likelihood of hypoxia. These include antenatal clinical markers (such as fetal movements, and meconium staining of liquor), bedside measures carried out peripartum (such as cardiotocography and fetal electrocardiogram (ECG) and blood gas analysis[49]. These are indirect and often subjective markers and have been criticised as poor predictors of HIE[50].

1.2.3.1 Reduced fetal movements

Maternal perception of normal fetal movements correlates well with the health of the fetus[51] and is used as part of the routine monitoring of fetal wellbeing during pregnancy. Women are asked to report reduced fetal movements to their midwife. Reduced fetal movements have been shown to be associated with a number of adverse outcomes including stillbirth[52]. There is limited evidence regarding the utility of reduced fetal movements as a marker of hypoxia- ischemia[53]. A Cochrane review[54] concluded that more studies are needed. The existing evidence suggests that maternal awareness of fetal movements is a more useful marker than the number of movements[53].

1.2.3.2 Meconium staining of liquor

Fetal passage of meconium is seen in 12%–22% of all pregnancies[55]. It is associated with other factors such as postmaturity, intrauterine infection and chorioamnionitis. It may be a sign of fetal hypoxia or acidosis although studies are limited to relatively dated retrospective studies which are only able to show association rather than causation; the pathophysiology of fetal meconium passage may relate to in-utero relaxation of the anal sphincter or vagal stimulation[56].

A large retrospective case-control study[57] of meconium staining (165 neonates with meconium stained liquor; 190 randomly selected controls without meconium stained liquor) in India reported a statistically significant increased risk of “birth asphyxia” in the group with meconium stained liquor (15.2%) compared to 5.3% in the control group. At first sight this result supports the previously reported association. However it is difficult to appraise the validity of this study as the definition of “birth asphyxia” that they used in the study was not reported. Furthermore it is difficult to apply the findings locally as HIE in low resource countries such as India is known to have different characteristics, such as higher incidence of HIE due to intrapartum causes, compared to that seen in high resource countries.

1.2.3.3 Fetal heart rate measurement and cardiotocography (CTG)

Fetal heart rate is measured using intermittent auscultation and by continuous recording of the cardiotocograph (CTG) (uterine contractions as well as the fetal heart rate, and patterns of fetal heart rate such as variability, accelerations and decelerations). In the UK intermittent auscultation of the fetal heart rate every fifteen minutes is offered to all women in established first stage of labour according to National Institute of Clinical Excellence (NICE) guidance[58], while CTG is offered to women who are have risk factors for fetal distress, such as passage of meconium.

Correlations have been demonstrated between CTG and other markers of fetal distress. For example a large retrospective case-matched control study of electronic fetal heart rate interpretation in 240 infants[59] found that electronic interpretation of the fetal heart rate led to statistically significantly earlier identification of fetal acidemia. However this study did not report the more clinically relevant outcome of HIE so its clinical significance is unclear. Overall, fetal heart rate measurement and cardiotocography do not correlate well with the development of HIE[60]. This may be related to the finding that the interpretation of CTG is subjective with poor intra and inter observer agreement [61,62,63,64,65,66].

1.2.3.4 Fetal electrocardiogram (ECG)

Fetal electrocardiography is a measurement of the electrical activity of the fetal heart and can be performed as a single assessment or as continuous electronic monitoring. The fetal electrocardiogram may be altered in hypoxaemia, showing, for example, paradoxical shortening of the PR interval during fetal bradycardia and the elevation or depression of the ST segment[67]. Evidence for the utility of fetal ECG as a marker of hypoxia is limited, with a Cochrane review[67] of seven large studies of fetal ECG concluding that there is little strong evidence that ST waveform analysis has an effect on the number of babies with neonatal encephalopathy (RR 0.61, 95% CI 0.30-1.22). Since this review a well powered cohort study of 260 infants[68] found that the rate of operative delivery for fetal distress was significantly lower in the group monitored with CTG together with ST interval analysis of fetal ECG, than in the group monitored with CTG only. This result is interesting; however it needs replication before it can lead to a change in clinical practice as it is potentially biased by the unblinded use of fetal ECG.

1.2.3.5 Blood gas analysis

Blood gas analysis is a bedside test used to measure the pH and partial pressures of oxygen and carbon dioxide in the blood and reflects gas exchange. It can be performed in utero (fetal blood sampling), from umbilical arterial or venous blood, or from infant arterial, venous or capillary sampling after birth.

In HIE, hypoxia-ischaemia is sometimes associated with abnormal gas exchange[69] and hence blood gas analysis may indicate acidemia and acidosis due to impaired gas exchange leading to hypoxia and hypercapnia, and/or lactatemia. However acidemia does not correlate well with the development of HIE[70] perhaps because impaired gas exchange does not always lead to HIE as the fetus may maintain normal cerebral blood flow by compensation. In addition HIE may occur in the absence of impaired gas exchange16 (for example if the umbilical cord is acutely impinged, prolapsed, or tightly wound around the fetus's neck, the cord blood gas may be normal).

A large prospective cohort study of 297 infants with neurological, haemodynamic or respiratory signs at 30 minutes of life[69], found that a base deficit of 14 mmol/l on blood gas analysis at 30-45 minutes of life corresponded with sensitivity of 73.2% and specificity of 82% for moderate - severe NE identified clinically at 30 minutes of life. However the early timing of neurological assessment in this study may have led to overdiagnosis of transient neurological abnormalities as HIE and in turn overestimation of the specificity of the test.

1.3 Investigations

There is no single investigation that can be used to diagnose HIE. However a number of investigations can provide supportive information regarding fetal hypoxia and/or neonatal brain injury.

1.3.1 Laboratory tests

Infants with HIE may suffer from hypoxia-ischaemia to organs other than the brain. Evidence from animal studies two decades ago has strongly suggested that this is due to the diving reflex involving shunting of blood away from other organs in order to maximise perfusion of the brain[27]. The diving reflex is inconsistently activated in HIE leading to the varied reports of involvement of other organs[16]. Although some studies have hypothesised that hypoxia to other organs might cause brain hypoxia, this phenomenon has not been demonstrated in vivo[72,73]. In addition there may be confounding due to organ dysfunction related to therapeutic hypothermia.

1.3.1.1 Acute kidney injury

Acute kidney injury may occur in HIE because renal parenchymal cells have a limited capacity for anaerobic respiration and a high susceptibility to reperfusion injury[74]. The incidence of acute kidney injury in HIE is however unclear. Results from a number of studies suggest that an estimated 50-72% of infants with a five minute Apgar score ≤6 show signs of renal compromise [75,76] but these studies had a number of limitations: five minute Apgar score is a non specific marker of

HIE; sample sizes were small, and urea and creatinine are non-specific markers of renal dysfunction. This is likely to lead to overestimation of the incidence in HIE. Evidence from a single randomised controlled trial[77] of 120 infants in an Indian tertiary hospital found the incidence of acute kidney injury was statistically and clinically significantly lower in the treatment group (32% versus 60%, $p<0.05$). However this clinical setting is clearly very different from high resource countries (as therapeutic hypothermia is not a standard of care). Hence further studies in a more clinical applicable setting are required.

1.3.1.2 Coagulopathy

Infants with HIE may have coagulopathy due to ischaemia of the liver and bone marrow as well as the effects of therapeutic hypothermia on slowing enzymatic activity involved in the coagulation cascade. A recent retrospective observational cohort study of 98 infants with HIE in a North American specialist neonatal unit[79] found that abnormalities in coagulation (high prothrombin time and low fibrinogen) or platelets were present. However, the definition of an abnormal result was arbitrary as there is no established reference range for prothrombin time and fibrinogen in neonates. In addition, as this was a retrospective study of infants who had been clinically selected by the treating clinician as needing testing, there may be selection bias and it is not possible to estimate the incidence of abnormalities from this study.

1.3.1.3 Cardiac dysfunction

Cardiac dysfunction may arise in HIE if cardiac hypoxia-ischaemia develops despite the initial intrinsic mechanisms to protect blood supply to vital organs. A number of markers have been used to measure cardiac function in HIE, including direct measures such as echocardiography or requirement for volume support and indirect measures such as cardiac enzymes (eg creatine kinase - muscle type, troponin I, troponin T). With respect to the value of cardiac enzymes; neonatal reference ranges have been clearly defined and cardiac enzyme elevation is associated with poor prognosis; however the correlation between biomarkers and ventricular dysfunction has not specifically been well described[80].

Many of the studies use a mixture of heterogeneous markers of cardiac dysfunction making its incidence difficult to estimate. For example a study of 46 cases of HIE found that 78% had elevated circulating cardiac enzymes and/or the requirement of volume support for longer than two hours after birth[72].

1.3.1.3 Thrombocytopenia

Thrombocytopenia, which may result from bone marrow suppression during fetal hypoxia, has been found to be associated with fetal hypoxia[81] and in addition to be more common in infants who receive therapeutic hypothermia[82]; however no direct association with HIE has been found.

1.3.1.4 Liver dysfunction

During hypoxia the "diving reflex" leads to reduced hepatic blood flow through both the hepatic artery as well as the portal vein. Liver dysfunction has been found to be associated with fetal hypoxia in a number of observational studies; however the association between liver dysfunction and clearly evaluated HIE has not been well described.. For example an Indian case-control study of sixty- two infants with HIE (including mild as well as moderate-severe) found that thirty- five cases (56%) had elevated serum alanine aminotransferase (ALT) elevation beyond two standard deviations above the mean of control subjects[83]. Another case-control study in India[84] of 70 infants concluded that markers of liver dysfunction can be helpful in diagnosis of HIE although their results are limited to an association between markers of liver dysfunction and poor condition at birth. Both of these studies were limited by heterogeneous groups of cases including infants of no or various degrees of brain dysfunction.

1.3.2 Electroencephalography

Electroencephalography (EEG) measures electrical activity in the brain arising from action potentials generated by neurons. The normal neonatal EEG consists of background electrical activity which has a characteristic amplitude, frequency, symmetry, synchrony and sleep wake state. During encephalopathy real time changes may be seen in this background and in addition epileptic seizures may be present.

1.3.2.1 Amplitude-integrated EEG

Amplitude-integrated EEG (aEEG) is a technique that has been developed from EEG. The raw EEG is filtered and compressed to simplify interpretation, carried out by measuring changes in amplitude of the EEG measured in microvolts (mV) e and the impedance between the recording electrodes. Cerebral function monitors (CFM) are used to record the aEEG at the bedside. By combining the pattern of the tracing together with measurement of the amplitude[85,86], clinicians can interpret the aEEG using pattern recognition[87] allowing widespread easily accessible bedside neurophysiological testing[88]. The amplitude-integrated EEG in infants with HIE has been found to correlate well with the clinical grading of HIE[89].

1.3.3 Neuroimaging

1.3.3.1 Cranial ultrasound

Cranial ultrasound is a technique which uses high-frequency sound waves emitted by a probe placed on the anterior fontanelle. The relative rate of reflection of sound waves by different types of tissues is used to create an image of the brain. Compared to other imaging techniques such as CT and MRI, it has limited sensitivity and is both equipment and operator dependent but, has the advantage of availability at the bedside[90]. In HIE cranial ultrasound may show increased echogenicity or brightness of the thalamus[91] or cerebral oedema[92]. Adjunctive

imaging techniques such as Doppler may be abnormal from the second day onwards in severe HIE[93,94,95] although the appearances may be affected by hypothermia[94].

1.3.3.2 Magnetic resonance (MR) imaging

Magnetic resonance (MR) imaging began to be developed in the 1980s and is now available in most hospitals in the UK. In MR imaging the patient is placed in a static magnetic field and subjected to a radiofrequency pulse causing hydrogen protons in the patient to become aligned and then misaligned with the magnetic field. The radiofrequency pulse is then dissipated causing the hydrogen protons to re-align with the magnetic field, generating an MRI signal as they do so. Smaller ("gradient") magnetic fields are applied which perturb the main magnetic field and cause hydrogen proton precession at rates according to their location allowing spatial location of the MRI signals, generating an image.

1.3.3.2.1 Conventional MRI

Characteristic changes are seen on conventional MRI in the second week of life[96,97,98]. Imaging findings vary with brain maturity, severity of injury and timing of imaging[98]. There are two common patterns of MRI changes in HIE. In acute profound hypoxia, abnormal signal in the basal ganglia and thalamus has been observed and in term infants predominantly affects the central grey nuclei and perirolandic cortex bilaterally and sometimes the hippocampus and brainstem. In chronic partial hypoxia, abnormal signal has been observed in the watershed areas (i.e. areas with least blood supply and hence most vulnerable to hypoxia). This is mainly the white matter and, in more severely affected infants, also the overlying cortex in the vascular watershed zones (anterior-middle cerebral artery and posterior-middle cerebral artery). Although the sensitivity and specificity have not been formally evaluated, Volpe[7] estimated that the MRI shows characteristic abnormalities in 50-85% of moderate-severe HIE with combinations of abnormalities of basal ganglia/thalamus, cerebral cortex (especially peri-Rolandic cortex), parasagittal (watershed) cortex and white matter, cerebral white matter primarily, and brainstem.

1.3.3.2.2 Diffusion weighted imaging

In HIE cytotoxic oedema occurs within hours of injury, represents the redistribution of water from extracellular to intracellular compartments, without a change in local constituents, and hence cannot be detected by conventional MRI. Diffusion weighted imaging (DWI) is an imaging technique which uses MRI to measure the magnitude of diffusion of water molecules through tissues measured as an apparent diffusion coefficient (ADC). Unlike conventional MRI, DWI is able to detect cytotoxic oedema which occurs within hours of HIE brain injury. As water moves from the extracellular to the intracellular compartment, there is a commensurate decrease in diffusion, identified as high signal on DWI and low signal on ADC. Changes are seen on the first or second day after injury[98] and are maximal at four days after injury[100]. There may follow a period of "pseudonormalisation" of DWI, beginning at the end of the second week and persisting for 6 to 10 days as the cytotoxic oedema resolves while the underlying brain injury evolves[100,101].

1.3.3.2.1 MR spectroscopy

MR spectroscopy is an adjunctive technique used alongside MR imaging that uses magnetic resonance signals to detect metabolites[102,103]. It uses the slight difference in resonance frequency between metabolites due to the difference in valence electrons around the protons to generate peaks for each metabolite, within a region of interest within the brain. In HIE there may be an elevated lactate peak or high lactate/choline ratio in the basal nuclei.

1.3.3.2.2 MRI in preterm infants following fetal hypoxia

MRI findings in preterm infants have been less well studied than those in term infants. The limited evidence suggests that there are similar MRI changes with a preponderance of white matter changes. For example a small study[104] found severe basal ganglia changes in 75% and mild white matter changes in 89%. It is unclear whether the relatively high prevalence of white matter changes is real

(as studies are few and limited) and whether it reflects chronic partial hypoxia or white matter injury secondary to prematurity.

1.3.3.2.3 Prognostic value of MRI

MRI has been found to be of good prognostic value in a number of studies[105,106,107]. For example a meta-analysis[108] found that in moderate HIE certain conventional MRI changes are associated with very severe adverse outcomes (i.e. death, severe developmental delay/spastic quadriplegic cerebral palsy/dystonic cerebral palsy) with a likelihood ratio of 5.0 (CI 2.3 – 10.6) and positive predictive value of 59-91%. This wide confidence interval and large range for PPV may be due to the heterogeneity between studies and the variability in MRI imaging and reporting equipment across studies.

1.3.4 Placental and cord studies

The placenta is a materno-fetal organ. During fetal life the umbilical cord and placenta connect the fetus to the mother and blood passes through them to deliver oxygen to and other materials to and from the fetus. The cord is approximately 60cm in length and contains two umbilical arteries and one umbilical vein. Its vessels branch out over the surface of the placenta and further divide to form a network covered by a thin layer of cells. The placenta is usually disc shaped, 22cm long and 2 cm thick. It is composed of the chorionic fetal membrane organised in villi (projections) in close apposition with the maternal blood vessels to optimise physiological exchange processes such as diffusion of oxygen. The cord is cut during delivery. The remainder of the cord and the placenta is delivered after the infant and may be studied macroscopically as well as histologically. Characteristic macroscopic and histological changes may be seen following hypoxia[109,110,111,112]. These changes have been categorised with regard to the timing of the fetal compromise[109]. They also have been characterised further with regard to their correlation with the brain MRI changes associated with HIE[111]. This study found that chronic villitis was associated with basal ganglia and thalamus injury characteristic of acute hypoxia while decreased placental maturation was associated with white matter injury.

1.3.5 Post mortem studies

Post-mortem examination, or autopsy, in order to determine the cause of death, may be performed by invasive (pathological and histo-pathological) and non-invasive (magnetic resonance) techniques. Characteristic changes, addressed below, have been observed at post mortem in HIE[113] and post mortem is particularly helpful in conditions such as this where there is no diagnostic gold standard[114]. For example a small study of 20 infants (37 or more weeks gestation) who had died in the neonatal period with a clinical diagnosis of grade 3 HIE in a tertiary New Zealand neonatal unit[113] found that all twenty infants had histological autopsy findings consistent with HIE. They can also be helpful in identifying previously unidentified co-morbidity in infants thought to have died from HIE. For example in the observational study described above[113] ten infants (50%) were found to have previously unsuspected co-morbidities at post mortem examination: fetal malnutrition, old CNS lesions, congenital infection, and severe intracranial trauma. The sensitivity and specificity of post mortem changes is unknown as, due to the nature of the subject, studies are subject to selection and observer bias[114,115,116,117]. Due to their nature, post mortem studies are small, partly due to the difficulty of obtaining consent from recently bereaved families, unblinded, and include only infants who had severe HIE leading to neonatal death. In addition there can be difficulties in interpretation arising from storage and preservation techniques[117]. Post mortem MRI, whilst non-invasive, is not be as specific as histological examination. A very small case control study of 14 infants[118], of which seven had been clinically diagnosed to have NE, and seven had been clinically identified as sudden unexplained neonatal death, showed no difference in post mortem brain MRI between cases and controls. Whilst very limited in size and scope, this study is helpful in identifying the potential difficulties in studying post-mortem changes in HIE using MRI.

1.4 Management

1.4.1 Therapeutic hypothermia

Therapeutic hypothermia is a method of targeted temperature reduction aimed at reducing or preventing the second wave of injury to the brain by reducing the metabolic rate and ameliorating the consequent oxidative stress[43]. A number of methods of therapeutic hypothermia have been trialled; whole body cooling (using cooling blankets)[43,44], selective head cooling (using cooling caps with circulating water)[119], and low resource adapted methods of cooling[120]. Whole body cooling is now a standard of care in moderate-severe HIE[121]. Twelve years ago it was shown in two large randomised controlled trials that therapeutic hypothermia using whole body cooling blankets (cooling to a target of 33.5^{O}C +/- 0.5^{O}C) for 72 hours in infants with moderate to severe HIE commenced within six hours of life decreases death and moderate to severe disability at 18 to 22 months[43,44]. This has been replicated many times and there is now evidence from at least eleven randomized clinical trials indicating that therapeutic hypothermia reduces mortality and long-term neurological morbidity rates by 15% (95% confidence interval [CI] 10–20%) and reduces the risk of CP by 12% (95% CI 6–18%), with a number needed to treat of 8 (95% CI 5-14)[122]. Furthermore it has been shown that the benefits of treatment persist at 6 to 7 years of age[123]. Since publication of the results of the TOBY[43] trial, neonatal services in the UK have adopted routine use of the TOBY diagnostic criteria (Table 1.1) to diagnose HIE. Infants who are diagnosed with moderate or severe HIE usually require therapeutic hypothermia, classified as intensive care[124]. If this therapeutic hypothermia is not available at the centre of birth, infants are transferred to a centre that is able to offer this therapy. Therapeutic hypothermia for moderate-severe HIE is classified as intensive care[124] i.e. care provided for babies who are the most unwell or unstable and have the greatest needs in relation to staff skills and staff to patient ratios[124] due to the monitoring and expertise required to provide therapeutic hypothermia. These infants also have additional care needs relating to the possible risk of seizures and multiorgan failure.

1.5 Complications of HIE

Moderate to severe HIE has a number of complications. Twenty to almost 40% of infants die in the neonatal period following HIE[123,124,125] about 20% develop a severe disability such as cerebral palsy[123] and 10% develop moderate impairment in motor or cognitive function later in life[123]. Globally, an estimated 287,000 (181,000–440,000) neonates with NE died in 2010; 233,000 (163,000–342,000) survived with moderate or severe neurodevelopmental impairment; and 181,000 (82,000–319,000) had mild impairment. In the Global Burden of Disease study GBD2010, intrapartum-related conditions comprised 50.2 million disability-adjusted life years (DALYs) (2.4% of total) and 6.1 million YLDs.

1.5.1 Neonatal death

HIE is a significant cause of neonatal death worldwide. The WHO has identified birth asphyxia defined as the full-term baby who is not breathing and in poor condition at birth with an assumed association to acute intrapartum event as the cause of 23% of neonatal deaths[1]. This figure clearly includes a heterogenous group of infants including some HIE and is also likely to be skewed by the relatively high incidence of all–cause death as well as death due to HIE in infancy in low resource countries. For example a large prospective observational study[127] of 4720 births over one year in rural Tanzania, a low resource country, found a relatively high incidence of all-cause death (10.3 per 1000 live births) as well as death due to HIE (6.3 per 1000 live births).

1.5.2 Cerebral palsy

Cerebral palsy (CP) is a static motor impairment caused by an insult to the developing brain during the fetal, neonatal or early childhood period. The prevalence of cerebral palsy was estimated in a US study to be 1.5—4.0 per 1000 live births[128]. A similar estimate of 2-2.5 per 1000 live births was obtained in the last UK study of prevalence although this was 20 years earlier[129]. In a recent study nearly one of every five infants who received therapeutic hypothermia for

moderate to severe HIE developed cerebral palsy[130]. Cerebral palsy following HIE tends to be of the spastic quadriplegic or dyskinetic types.

For many years it was assumed that cerebral palsy arising in the neonatal period reflects fetal hypoxia. However it has become clear that there are many causes of cerebral palsy other than hypoxia. For example, an estimate based on retrospective application of the American College of Obstetricians and Gynaecologists / American Academy of Pediatrics criteria to identify acute intrapartum hypoxia in 213 neonates with CP in one South Australian tertiary hospital estimated that intrapartum hypoxia was the cause in only 10% of CP[132]. This study included a large representative sample (213 out of 235 consecutive neonates diagnosed with CP over 17 years). There may have been reporting bias of markers of intrapartum hypoxia as the study was not blinded so observers were aware of the neurological morbidity of the infants, and its clinical applicability may have changed over the long time period required to obtain the sample. Another group estimated that peripartum (antepartum or intrapartum) hypoxia was the cause in 30% of CP [119]. In the majority of cases in both these studies, CP was thought to arise from insults to the developing brain other than HIE.

1.6 Literature overview and identification of gaps in the literature regarding epidemiological case definitions and aetiology of HIE

1.6.1 Search strategy

A literature overview was conducted in order to examine the epidemiological and aetiological aspects of NE and HIE. The OVID 1948- present and Embase databases were searched using the following search terms:- “Asphyxia neonatorum”, Or “Hypoxia-ischemia, Brain”, Or Fetal distress” or “Foetal distress”, Or “Fetal asphyx*” Or “Foetal asphyx*”, Or “Birth asphyx*” Or “Newborn asphyx*” Or “Hypoxic ischaemic encephalopathy” Or “Hypoxic ischemic encephalopathy” Or “Newborn encephalopath*” Or “Perinatal encephalopath*” Or “Neonat* encephalopath*” Or “Infant encephalopath*” Or “Seizure*” and “neonat*/newborn” Or “Encephalopathy” and “neonat*/newborn” with the following limits: English language, Humans, 1970-May week 2 2011. This yielded

11116 results. Of these I reviewed abstracts of all review papers for possible inclusion in my literature overview. I then carried out the same search with the following limits: English language, Humans, 2006-May week 2 2011. this yielded 2546 results.. Following manual review of the abstracts of these papers, recent original papers, these papers and referenced papers, relevant to defining features or aetiology of HIE were used to inform the following overview of the subject. A systematic review of the literature would be beyond the scope of this project, so systematic review protocols were not followed.

1.6.2 Existing epidemiological case definitions of HIE used in public health surveillance of HIE

Data registry use in HIE has been recommended for infants receiving therapeutic hypothermia since it began to be used[133]. A number of surveillance methods have been used for surveillance of HIE. A number of case definitions of HIE used in the public health surveillance of HIE are discussed. Clinical definitions, described in section 1.3 are not described here.

Table 1.4: Epidemiological definitions of HIE

Author	Definition of hypoxia-ischaemia	Definition of encephalopathy
Collaborative Perinatal Project (1953)[133]	Either lowest FHR <60 beats per minute	Or five minute Apgar <3, or time to first cry >5 minutes.
The Neonatal Survey (NE)[134] 2011 (unpublished manual)	None	convulsions and requires medication or convulsions requiring ventilation and medication or ”flat at birth” and require ventilation due to asphyxia but do not develop convulsions
Vermont Oxford Network 2006[135] (NE)	Either five minute Apgar score <=3	Or infants of ≥ 36 weeks with seizures or altered consciousness (stupor, coma) during the first 72 hours of life , or receiving therapeutic hypothermia.

There have been many definitions of HIE and similar conditions such as “neonatal encephalopathy” and “birth asphyxia” used in international surveillance over the years. As can be seen from the table above these definitions vary widely in terms of the evaluation of hypoxia and/or encephalopathy. Clearly many definitions make assumptions about aetiology[5] and this may lead to inappropriate evaluation of these two key components and consequently discrepancies in trends identified by differing surveillance methods. One of the first definitions was that of birth asphyxia by the Collaborative Perinatal Project[134]. Many of them are very brief, clear, objective and can be recorded by non-clinical staff which is particularly useful in low resource settings. However simplicity of criteria may also mean that infants with relatively severe HIE are included and infants with moderate HIE who do not have seizures but have other features of moderate encephalopathy are excluded. In addition infants with NE which is not due to hypoxia but other aetiologies such as preterm birth, infection, maternal analgesia, congenital malformations, or metabolic disorders, may be included, although some criteria e.g. Vermont Oxford Network[136] have excluded infants with central nervous system birth defects and congenital anomalies. This makes the assumption that these infants do not have HIE; this may lead to underestimation of true prevalence[16]. Some registries eg the New Zealand Paediatric Surveillance Unit[137] have taken a prospective approach and taken measures to improve case ascertainment by contacting key clinicians; this has a number of advantages although there are high administrative costs to such a system.

Locally, data was collected on the incidence of neonatal encephalopathy by The Neonatal Survey (formerly Trent Neonatal Survey), a regionally commissioned audit of neonatal care in the East Midlands, South Yorkshire and South Humber, for 25 years between 1990 and 2014. The trends it identified with regard to incidence of neonatal encephalopathy were used to underpin clinical governance in relation to neonatal intensive care services. As the definition it uses is a simple one for all the reasons above, it too has the potentials for bias given above. In the UK, clinicians submit patient data for infants receiving therapeutic hypothermia to the UK TOBY cooling register. This is a voluntary, centralised register of all infants receiving therapeutic hypothermia with participation from neonatal units. It has the limitation that participation is voluntary and there is

susceptibility to many sources of bias, but with awareness and recognition of this, its data may be useful for planning clinical research and guiding clinical policy in HIE.

1.6.3 Existing knowledge about the aetiology of HIE

The aetiology of perinatal brain injury was first postulated by the orthopaedic surgeon William Little and the child psychiatrist Sigmund Freud in the middle of the twentieth century[138]. Little believed that events associated with birth were causally associated with brain injury (both CP and severe learning disability) while Freud believed that abnormal fetal development led to both events at birth and neurodevelopmental impairment[138]. Little's assumptions have persisted to the modern day in HIE as well as CP, with markers of intrapartum hypoxia being encompassed in most definitions of HIE. Initially it was assumed that HIE was a consequence of intrapartum hypoxia alone and this was reflected in some of the outdated terms used to describe it such as "birth asphyxia". However over time it is becoming clear that the aetiology of HIE is more complex than this as there are many unanswered questions. There may after all be a role for fetal development as Freud postulated. Why do all infants subjected to hypoxia not develop HIE? Why does one infant who appears to have been subjected to mild hypoxia, develop severe HIE, while another subjected to severe intrapartum hypoxia does not develop HIE at all? What are the susceptibility factors involved?

1.6.3.1 Role of intrapartum hypoxia

Although HIE is defined by perinatal hypoxia-ischaemia and the consequences of this have been studied in detail, the scope of the nature and timing of the hypoxic-ischaemic insult is poorly understood. The available data is largely from studies of cohorts selected for certain characteristics with unknown validity (such as neuroimaging characteristics) rather than truly representative population-based studies, with resulting vulnerability to selection bias. In low resource countries intrapartum hypoxia is likely to be the most significant aetiological factor and this is reflected in the much higher incidence of HIE in low resource countries and the effectiveness of measures to reduce intrapartum hypoxia. In high

resource countries, there is a sizeable body of evidence from a number of large studies to support a strong correlation between markers of intrapartum hypoxia-ischaemia and HIE. Therapeutic hypothermia trials have estimated the proportion of infants with HIE with intrapartum acute hypoxic events, at 40% to 60%[44,122]. A large case control study[139] of 261 infants diagnosed clinically with NE and 90 infants with seizures but clinically not thought to have NE found that there were changes suggestive of an acute insult on MRI or post mortem imaging in 80% of the encephalopathic infants and none of the controls. In the group with seizures only, focal damage (stroke) was found in 69% while 2% had evidence of antenatal injury. This study showed there was no MRI evidence of antepartum hypoxia-ischaemia in this population and has been quoted as evidence that antepartum factors are not involved in the pathogenesis of the majority of HIE, although the sensitivity of MRI in detecting antepartum hypoxia is not known. In addition this group was a selected group of infants with relatively severe HIE from a specialist centre and cannot be generalised to all infants with HIE without further study (66 infants in the encephalopathic group died and 85 had neurological sequelae).

In animal studies hypoxia-ischaemia has been simulated by reducing the blood supply to the fetal animal brain during the intrapartum period in an acute total or chronic partial way. Whilst this enables direct measurement of the extent of hypoxia and ischaemia and the response to it, it makes a number of assumptions, primarily that in human HIE hypoxia occurs in one of these ways to a previously healthy fetus. Human studies enable more direct application of the results to human HIE. However there are three main groups of challenges to human studies[131]. Firstly unlike in animal studies it is not possible to measure hypoxia ischaemia directly. This means that indirect assessments are required. These may include the biophysical profile, fetal heart rate measurements, fetal, cord or neonatal blood gas analysis, Apgar scores, and the neurological condition of the neonate. Secondly the timing of the hypoxic ischaemic event is often unknown and not possible to determine. Thirdly, there is no single highly sensitive and specific “gold standard” test to identify neonatal encephalopathy arising as a result of hypoxia-ischaemia.

1.6.1.2 Markers of hypoxia

In 1999 a template was defined by the Perinatal Society of Australia and New Zealand in order to better identify cases of cerebral palsy where the neuropathology began or became better established around labour and birth[131]. This incorporated only one marker of hypoxia: acidemia in fetal, umbilical arterial cord, or very early neonatal blood samples (pH <7.00 and base deficit <12 mmol/l). However many of these markers were previously found to be only weakly associated with HIE[50]. This study is subject to information bias as factors previously assumed to reflect hypoxia tend to be studied disproportionately. Factors thought to reflect hypoxia might reflect pre-existing neurological abnormality e.g. abnormal fetal heart rate[140]. No single indirect marker has been found to show a strong correlation, which may reflect the complex interaction between the hypoxia-ischaemia and the fetal adaptive response.

Volpe[7] compiled a list of markers of intrapartum hypoxia and categorised them into groups as process-based indicators, clinical-sign based indicators and outcome-based indicators. They include fetal heart rate abnormalities, fetal distress, acute sentinel events, umbilical arterial acidemia, low Apgar scores, need for respiratory support. These criteria are detailed but consequently not easy to use quickly and objectively to identify infants needing treatment. Volpe's overview is a non-systematic review and may be susceptible to reporting bias. For example, it omits factors such as laboratory markers of hypoxic injury to other systems, while including the Apgar score which has been shown to be a non-specific symptom-based measure in other studies[50].

1.6.1.3 Aetiological factors other than intrapartum hypoxia

While there is strong evidence for intrapartum timing in many cases of HIE, all of these studies have identified a group of infants who did not have evidence of intrapartum hypoxia[44]. Volpe[7] estimated that 35% of infants with NE have an intrapartum cause alone, 35% have both an intrapartum and antepartum cause, 20% have insults related primarily to antepartum events, and 10% had issues in the postpartum period (the latter was encountered primarily in prematurely born

infants). This might indicate inability to detect intrapartum hypoxia adequately; alternatively it might indicate a cause of HIE other than and/or in addition to intrapartum hypoxia.

1.6.3.3.1 Antepartum factors

The first large study to consider the possibility of aetiological factors other than intrapartum hypoxia was a large retrospective population-based unmatched case-control study was conducted of 164 infants with moderate or severe NE, in Western Australia over twenty years ago[142,143]. For the first time in such a study, the authors defined moderate-severe neonatal encephalopathy as either seizures alone or any two of the following lasting for longer than 24 hours: abnormal consciousness, difficulty maintaining respiration (of presumed central origin), difficulty feeding (of presumed central origin) and abnormal tone and reflexes without a marker of hypoxia. In addition they defined criteria for exposure to possible intrapartum hypoxia as presence of an abnormal intrapartum cardiotocogram or abnormal fetal heart rate on auscultation or fresh meconium in labour or both, together with a one minute Apgar score of less than 3 and a five minute Apgar score of less than 7. Intrapartum hypoxia fulfilling these criteria was identified in 19% of infants with neonatal encephalopathy. A further 10% of infants with neonatal encephalopathy were found to have "evidence that they had experienced a significant intrapartum event which had been associated with intrapartum hypoxia". Hence markers of intrapartum hypoxia were found in a total of 29% of infants with neonatal encephalopathy in this study, in comparison with 0.5% of unmatched controls. Statistically significant associations between NE and a number of factors were found: increasing maternal age, decreasing parity, poorer socioeconomic status, family history of seizures or neurological disease, infertility, maternal thyroid disease, and bleeding in pregnancy. Unlike preceding epidemiological studies this study did not make assumptions about the causation of NE: the inclusion criteria relate only to the clinical syndrome of disordered brain function. This allowed analysis of the relative contribution of markers of antepartum and intrapartum hypoxia, although as the study was retrospective it is not possible to deduce whether HIE was caused by antepartum factors in those infants who had NE and markers of antepartum hypoxia.

The second observational study to investigate these associations further was an Italian case-control study of 27 infants with NE and 100 controls [144]. They used attending neonatologists' clinical diagnosis of NE with improved accuracy compared to retrospective criteria used in many other studies. Unlike the Western Australian study[142] they excluded infants with other causes of NE. As this study was very small there is a risk of overestimation of associations; they found that 26% of cases of NE had only antepartum risk factors, 22% had only intrapartum risk factors, and 44% had a combination of the two. While this result appears to add to evidence for both intrapartum and antepartum factors, this was a very small study with a high risk of bias.

The next large study in this field was a large case-control study of 405 cases and 239 controls in London[145]. In this study HIE was defined as poor condition at birth (5minute Apgar score <5 and/or arterial cord blood pH <7.1 and/or need for major resuscitation) and NE of any severity; 77.5% had moderate-severe HIE. In contrast with the Western Australian study, this study excluded infants with an identifiable metabolic disorder, severe congenital malformation, or infection or genetic abnormality. They found a much lower proportion of infants with antepartum factors only; 6.7% of cases. They found that 69.5% of cases had intrapartum as well as antepartum factors and 20% of infants with HIE had only intrapartum factors. The authors of the study concluded that the absence of antepartum factors in this cohort pointed to the intrapartum period as the necessary factor for HIE. Whilst this is one possible explanation, it is also possible that the inclusion and exclusion criteria are lead to selection bias and a sample that is likely to be over-representative of infants with isolated HIE and under-representative of infants who have both HIE and NE due to another cause.

The most recent large study of the aetiology of HIE was a large Swedish retrospective cohort study[20] of 46749 infants of whom 79 were diagnosed with HIE. The criteria in the supplementary material are not yet accessible; no exclusion criteria with regard to morbidity are mentioned in the main body of the paper. Further information about inclusion and exclusion criteria is needed to

interpret these results. This study found statistically significant associations between HIE and abnormal CTG, and acute obstetrical events.

1.6.4 Gaps in the existing literature

There is a wealth of existing literature about HIE and NE. The existing studies use a number of definitions of HIE with a lack of consistency and clarity which can lead to inaccuracies in estimating incidence and interpreting incidence trends. There is a lack of direct evidence about the nature and timing of the hypoxic-ischemic insult. Many of the aetiological studies to date are limited in their assumption that the hypoxic-ischaemic insult can be measured using unvalidated markers, leading to selection bias.

1.7 Further steps

Following identification of the above gaps in the literature in the definition and aetiology of HIE, this study was planned with the aim of exploring the defining features of HIE for epidemiological use and the aetiology of HIE. A number of potential study designs to achieve this aim were explored, together with the relative merits and disadvantages associated with each.

In the first instance a prospective cohort approach was planned as it would have many advantages. Such an approach would avoid assumptions and recall bias, enable infants to be assessed in a standard way, by clinicians trained appropriately for the study rather than according to individual clinician's discretion allowing comparison between groups. It would allow measurement of incidence and study of causation of a relatively uncommon condition in order to determine the relative risks in an unselected representative population and to uncover unanticipated associations. The difficulties of a prospective study design included the length of time that it would take to obtain sufficient data and the cost associated with developing and conducting such a study in terms of appointing and training research staff, the unpredictability of births involving HIE, and the number of centres that would need to be involved, as this is a relatively uncommon condition. Collaborators were identified and research ethics

committee approval was obtained for such a study. Four funding grants were applied for in order to conduct the study prospectively. Unfortunately these applications were unsuccessful.

In the next instance a retrospective study design was considered. This could involve obtaining a representative sample of infants with possible HIE, retrospectively recording observations made and all possible aetiological factors, development of a reference standard by panel consensus, identifying cases of HIE using a reference standard, and describing possible aetiological factors in these cases. The main advantage of a retrospective study is that it entails less expense. Disadvantages of a retrospective study are that data from records not designed for the study may be of poor quality, there is frequently an absence of data on potential confounding factors, it may be difficult to identify an appropriate exposed cohort and an appropriate comparison group, and again there may be difficulty identifying sufficient cases of an uncommon disease and differential losses to follow up.

Following consideration of the relative advantages and disadvantages of each method, a retrospective approach was chosen, primarily on the grounds of cost.

Chapter 2: Aims and objectives

2.1 Aims

Exploratory study to examine epidemiological and aetiological aspects of NE and HIE and features that distinguish HIE from non-HIE NE.

2.2 Objectives

To develop a reference standard for diagnosis of neonatal encephalopathy (NE) and hypoxic-ischaemic encephalopathy (HIE) for use in this study by panel consensus

To identify and describe a sub-population of infants with NE and HIE according to the reference standard criteria

To develop an epidemiological case definition using this cohort

To estimate the validity of existing epidemiological case definitions.

Chapter 3: Methods

3.1 Introduction

Following identification of the gaps in the existing literature regarding case definition for HIE surveillance and the aetiology of HIE, the aims and objectives of the study were formulated as listed in Chapter 2. As described in section. a retrospective approach was adopted to achieve these aims and objectives.

3.2 Study design

3.2.1 Study planning

In order to design the study, a number of factors were taken into account. Published and unpublished sources of information were reviewed to gather information about the validity of the diagnostic criteria for HIE. Published sources were reviewed using a database search strategy as well as checking reference lists, citation searches, and hand searching. Information was obtained about current, potentially relevant issues identified by clinicians, epidemiologists and researchers. Locally there are two neonatal units: the Leicester Royal Infirmary and Leicester General Hospital. Experience of HIE definitions used in surveillance was discussed with neonatologists contributing data to The Neonatal Survey, neonatologists in London, and neuroradiologists in Sheffield and Nottingham. These discussions revealed several anecdotal instances of false positive diagnoses of HIE in infants who actually had non-HIE NE due to causes such as intracranial haemorrhage or metabolic disorders such as pyruvate dehydrogenase deficiency.

3.2.2 Identification of study population

3.2.2.1 Settings

In order to identify a representative population of infants, neonatal units were identified at hospitals across the East Midlands, Yorkshire & Humber and West Midlands regions of the UK. These neonatal units were selected to represent a range of levels of intensive care according to the Department of Health (2009) Toolkit for High Quality Neonatal Services. Neonatal units are classified according to a system devised by the British Association of Perinatal Medicine into 3 levels with respect to the level care provided (Table 3.1). The selected neonatal units are given in table 3.2. They were initially invited to take part by letter and email to the lead neonatologist and neonatologist(s) with an interest in HIE and all agreed to take part.

Table 3.1 : Department of Health designation of neonatal units (Department of Health 2009)

Level of neonatal unit	Description
Special Care Unit (SCU)	These provide special care for their own local population. They also provide, by agreement with their neonatal network, some high dependency services.
Local Neonatal Units (LNU)	These provide special care and high dependency care and a restricted volume of intensive care (as agreed locally) and would expect to transfer babies who require complex or longer-term intensive care to a Neonatal Intensive Care Unit.
Neonatal Intensive Care Unit (NICU)	These are larger intensive care units that provide the whole range of medical (and sometimes surgical) neonatal care for their local population and additional care for babies and their families referred from the neonatal network in which they are based, and also from other networks when necessary to deal with peaks of demand or requests for specialist care not available elsewhere. Many will be sited within perinatal centres that are able to offer similarly complex obstetric care. These units will also require close working arrangements with all of the relevant paediatric sub-specialties.

Table 3.2 : characteristics of initial six participating units

Neonatal unit	Level of neonatal care[145]
Leicester Royal Infirmary	Neonatal intensive Care Unit
Leicester General Hospital	Special Care Baby Unit
Leeds General Infirmary	Neonatal Intensive Care Unit
St James Hospital Leeds	Neonatal Intensive Care Unit
Kettering General Hospital	Local Neonatal Unit
Northampton General Hospital	Local Neonatal Unit

3.2.2.2 Identification of data sources

Data sources to identify an unselected population of infants with one or more features of suspected neonatal encephalopathy were identified. Routine data collection in neonatal units is carried out in both written and electronic formats. Electronic formats vary from those collecting mainly administrative information with a limited amount of clinical information such as the Electronic Discharge Information System, to those collecting detailed clinical information such as the Badgernet® neonatal database.

The Badgernet® neonatal database is a live patient data management system. Patient records are held centrally within secure hosted data centres and each distinct record is accessed on a controlled basis by all healthcare professionals in participating hospitals via a secure Badgernet® desktop application as well as an iPad App. There is no mandatory requirement but in many units the Badgernet® is completed regularly by junior doctors and checked by more senior doctors. The main weakness of Badgernet® is variable data quality control. On verbal enquiry, five out of the nine participating units reported having no quality control beyond single data entry by a senior house officer or above with intermittent quality checks by data officers, while four out of the nine participating units had routine checking and amendment of every discharge summary by a registrar and data officer.

In view of the relative strengths of the Badgernet® database as a data source described above, this was selected as the preferred data source for initial identification of the study population of infants with suspected encephalopathy. It was used as the data source in eight out of the nine units included. In the remaining unit the Badgernet® neonatal database was not in routine use and so the local data source (Electronic Discharge Information System), which had been in routine use during the study period, was used for case identification. As this is a more limited electronic neonatal database than Badgernet® this increased potential for case under-ascertainment.

3.2.2.3 Identification of time period

Consecutive admissions over a defined time period were studied in order to obtain an unselected population of infants and hence avoid selection bias. The initial time period chosen was December 2008 to December 2010. This was selected in order to allow a reasonable period of study along with time for up to two years' subsequent developmental follow-up, as many conditions which cause NE are often identified and many (although not all) of the complications of HIE are seen within the first two years of life.

3.2.2.4 Inclusion criteria

Neonatal discharge summaries were reviewed for every admission of at least 35 weeks' gestation to the participating NNUs during the study period. All infants with any of the following features of HIE within the first 96 hours of life were included (see box 3.1). In addition, the broadest gestation and symptom onset times described in the literature were applied, to include infants born at 35 or more weeks of gestation and symptom onset time up to 96 hours from birth.

Box 3.1: Inclusion criteria

Inclusion criteria

Inborn infants of at least 35 weeks gestation

Any one of the following symptoms within the first 96hours of life:-

- abnormal tone
- abnormal conscious level
- abnormal movements of limbs
- abnormal movements of eyes

3.2.2.5 Exclusion criteria

Outborn infants were excluded in order to avoid referral bias. Outborn infants transferred into a neonatal unit for further management of HIE were excluded as detailed information about the delivery and initial course was not available. Infants with congenital abnormalities were included in order to minimise selection and potential selection bias.

3.2.3 Sample size calculation

The sample size was calculated by using a process of iteration with various sample sizes and simulation to obtain the expected precision of the estimates for the sensitivity and specificity for each size of sample[146]. This method requires an assumed population prevalence of HIE within the cohort of infants with any features of encephalopathy. As there are no published estimates of this, an underlying prevalence of HIE of 50% was estimated. Repeated (10,000) samples were taken from the binomial distribution (n=45,p=0.50) to simulate the likely study sample. Within each of these samples the observations were designated as 'test positive' at random with probability of 0.7 for the 'true' positives (sensitivity) and 0.2 for the 'true negatives' (1- specificity). The observed sensitivity and specificity were then calculated for each sample and the difference

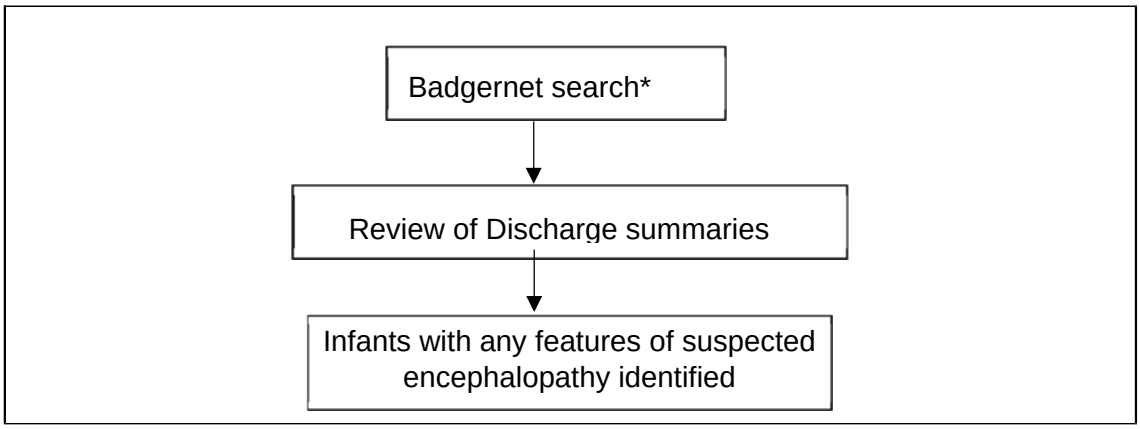
between the values for median and the 2.5th percentile for the sensitivity and specificity reported as the expected precision. It was found that, assuming a underlying prevalence of HIE of 50% and a true sensitivity and specificity of 70% and 80% respectively, and total sample size of of 300 giving 45 cases of HIE would allow the estimation of a 95% confidence interval for the sensitivity with a precision of ±19% and of ±17% for the specificity.

3.2.4 Pilot study

3.2.4.1 Methods

The aims of the pilot study were to examine the feasibility of the planned review of Badgernet® discharge summaries in order to identify infants with one or more symptoms of suspected encephalopathy. The objectives of the pilot study were to identify modifications needed in design of main study. The pilot study was conducted at the local neonatal intensive care unit, Leicester Royal Infirmary. The sample size was based pragmatically on time considerations. All Badgernet ® neonatal discharge summaries for infants of at least 35 weeks gestation admitted over a one year period (July 2011-June 2012) (both inborn and outborn) over a one year period were reviewed for features of suspected neonatal encephalopathy

Fig 3.1: Pilot study process



*Leicester Badgernet searched for all term (>35 weeks gestation) discharge summaries over 1 year period July 2011-June 2012

3.2.4.2 Results of pilot study

720 discharge summaries were identified and all were reviewed. The mean time taken to review the Badgernet® discharge summary was 2.9 minutes (SD 1.7). 94 (13.1%) infants had one or more features of suspected encephalopathy. 25 (26.6%) of these 94 infants had a diagnosis code of “Hypoxic-ischaemic encephalopathy”. 18 (19.1%) had transient features of HIE which resolved within the first hour of life often within the delivery room. Hence the pilot study suggested that Badgernet® discharge summary review was a feasible, time- effective way of identifying infants with any suspected encephalopathy.

3.2.4.3 Modifications to study following pilot study

The pilot study identified a number of modifications needed to the design of the study. Firstly it identified that a group of infants with transient signs of encephalopathy would be included by the present inclusion criteria. Hence the inclusion criteria were modified to allow for this. It was confirmed that for outborn infants detailed information about the delivery and initial course was not available in the Badgernet® summary. Hence the exclusion criteria were kept the same.

Box 3.2: Modified inclusion criteria

Modified inclusion criteria

Inborn infants of at least 35 weeks gestation

Any one of the following symptoms within the first 96hours of life, persisting beyond the first hour of life :-

- abnormal tone
- abnormal conscious level abnormal
- movements of limbs
- abnormal movements of eyes

Secondly, it identified that there was a relatively low estimated yield of infants with HIE (based on the Badgernet® codes) and there were fluctuations in data quality due to user experience as many units began to use the Badgernet® system during the planned study period (December 2008- December 2010). All units were contacted to establish their duration of experience using the Badgernet® electronic discharge summary system. This varied with the most recent start times being in mid 2009. The study period was then timed to begin in July 2010 so that the Badgernet® database had been in use for at least one year at the start of the study period in all units. This was done to assure a similar quality of data across the participating units. The end point of the study was extended as much as possible to allow the required two years followup ie June 2011. Hence the study period was changed to July 1st 2010 to June 30th 2011.

In order to increase the case yield in the face of the shortened study period, six additional neonatal units were invited to take part by letter and email to the lead neonatologist and neonatologist(s) with an interest in HIE. Five of these units agreed to take part, making total of eleven units (Table 3.3). One unit declined to take part but no reason was given.

Table 3.3 Characteristics of final eleven participating units

Neonatal unit	**Level of neonatal care[147]**
Leicester Royal Infirmary	Neonatal Intensive Care Unit
Leicester General Hospital	Special care baby unit
Jessop Wing Sheffield	Neonatal Intensive Care Unit
Leeds General Infirmary	Neonatal Intensive Care Unit
St James Hospital Leeds	Neonatal Intensive Care Unit
Royal Derby Hospital	Local Neonatal Unit
Kettering General Hospital	Local Neonatal Unit
Kings Mill Hospital Mansfield	Special care Unit -
Northampton General Hospital	Local Neonatal Unit
University Hospital Coventry	Neonatal Intensive Care Unit
George Eliot Hospital Nuneaton	Special Care Unit

3.2.4.4 Ethical approval

Ethical approval was sought from the NHS Nottingham (2) research Ethics Committee; further requested information and information regarding modifications was provided as requested, and approval was obtained (Appendix1). Approval from the National Information Governance Board (NIGB) and following its abolition the Confidentiality Advisory Group (CAG) of the Health Research Authority (HRA) was then obtained (see section 3.2.4.5 and Appendices 2 and 3). Local Research and Development (R&D) approval was sought from each of the ten sites, using Site Specific Information forms and following the process at each site (for example presenting to individual Trust Research Ethics Committees where required). Permission was sought from NHS Trust Research and Development departments associated with each of the eleven participating neonatal units to review maternal, neonatal and paediatric notes. This involved submitting an NHS to NHS proforma for confirmation of pre-engagement checks. Full permission followed by letters of access were obtained in ten units across eight Trusts. At the remaining one unit permission and a letter of access were obtained to review maternal and neonatal notes but not paediatric notes (Appendices 4-11).

3.2.4.5 Consent issues

Section 251 approval (ethics permission under the statutory power of Section 251 of the NHS Act 2006 (originally Section 60 of the Health and Social Care Act 2001)) was sought and obtained from the National Information Governance board (NIGB) (the predecessor of the Confidentiality Advisory Group, or CAG) and CAG in April 2013. This was done because informed consent would require contacting parents whose infants had had suspected encephalopathy and some of whom had unfortunately died. In this observational study this was likely to cause distress to them without having any potential for benefit for the individual child or family. Use of anonymised information was also considered and it was concluded that it would not suffice, as patient and mother identification and notes review would be required. The Section 251 approval meant that the common law duty of

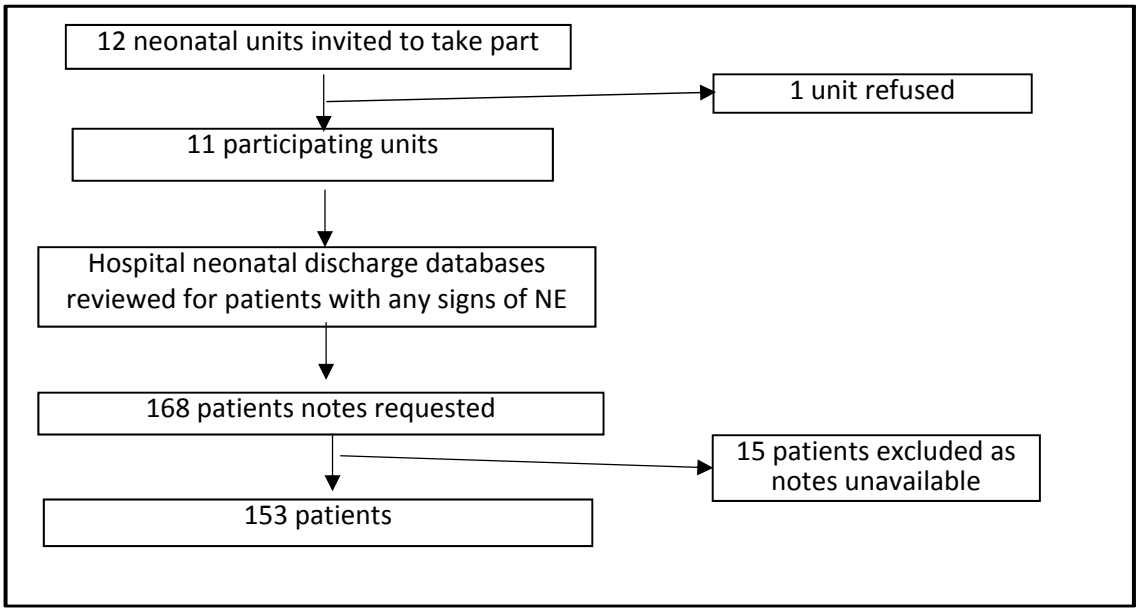
confidentiality was temporarily set aside and NHS patient identifiable information used (in compliance with the Data Protection Act of 1988) on the basis of the need to support essential NHS activity without the consent of patients.

3.3 Data collection

3.3.1 Identification of infants with any signs of suspected encephalopathy

At each participating neonatal unit discharge summaries written from July 1st 2010 to June 30th 2011 were manually reviewed to identify all infants fulfilling the inclusion criteria, ie 35 or more weeks gestation, with one or more of the following:- abnormal level of consciousness, abnormal tone, abnormal limb movements, and/or abnormal eye movements. Using these criteria, a total of 168 infants were identified as having one or more features of suspected encephalopathy.

Fig. 3.2 Flow chart to describe recruitment



3.3.2 Data collection

A proforma (Appendix 13) was designed to include a detailed description of all relevant clinical and aetiological factors. Antenatal and perinatal data were documented from the medical notes using the proforma. Demographic data included maternal age and race, and family history of seizures and/or neurologic disorders. By using information from the National Statistics Postcode Directory deprivation scores for every infant were obtained. The Index of Multiple Deprivation is a measure of multiple deprivation in a small area based on 7 dimensions: income, employment, health and disability, education, skills and training, barriers to housing and services, living environment, and crime. Higher scores reflect more disadvantaged areas. Maternal conditions included chronic hypertension, thyroid disease, depression, and thrombotic or autoimmune disease. Obstetric history included parity, previous history of miscarriages, and infertility treatment (any treatment to achieve the index pregnancy). Complications during pregnancy included gestational hypertension, respiratory or urinary tract infection, significant antepartum bleeding, and an episode of reduced fetal movements as reported by the mother before labour. All ultrasounds performed at 16-24 weeks gestation were classified as anomaly scans. CNS active drugs in labour included opiates and anaesthesia. Intrapartum factors recorded were: onset of labour, intrapartum complications, mode of delivery, Apgar scores, cord pH, and resuscitation measures. Prolonged rupture of membranes was defined as an interval of >24 hours between rupture of the membranes and delivery. Prolonged second stage was defined as a second stage of labour >2 hours.

Sentinel events included uterine rupture, placental abruption, cord prolapse, acute fetal exsanguination, and maternal collapse. Shoulder dystocia was defined as a delivery that required additional obstetric manoeuvres to release the shoulders after gentle downward traction had failed. Failed instrumental delivery (vacuum or forceps) was defined as the delivery of the infant by emergency Caesarean delivery after an attempted instrumental delivery had been unsuccessful. Elective Caesarean section was defined as a delivery undertaken before the onset of labour in which there was no current fetal concern.

Infant characteristics included gestational age, gender, birth weight, head circumference, and multiplicity. Growth centiles were calculated by using the WHO growth reference charts. Resuscitation was considered major if the infant required intubation for ventilation with or without cardiac compressions and epinephrine. Details of the clinical course, seizures, stage of HIE, and age at death were also collected. aEEG reports were classified according to the TOBY system. Where available raw aEEG was classified according to the TOBY aEEG pattern classification[84] as patterns 1-5 according to the background activity, minimum and maximum amplitude, voltage, and presence or absence of bursts. Cranial ultrasound images were reviewed if available. Reports were reviewed when images were not available. Resistive index was recorded as greater than or less than 0.55 and resistive index of 0.55 has previously been reported to be associated with HIE. Placental histology was categorised according to the findings associated with chronic in utero compromise, acute in utero compromise for less than 18 hours, and findings associated with subacute in utero compromise. MRIs carried out on day 1-4 were classified as “early” and MRIs done on day 5 onwards were classified as “late”. Again raw data was reviewed wherever available and reports were reviewed when raw data was not available. For infants who had undergone therapeutic hypothermia, information about alertness, tone, respiratory status, reflexes, seizures and feeding, before cooling was initiated and on days 1-4 of life was also collected from the UK TOBY cooling register observation forms.

Further information was obtained from obstetric letters and in those cases where infants died and post mortem was conducted, post mortem reports where these were available in the medical records. For infants transferred out of a study unit early in life, as much information as available about the subsequent course from the local notes (from written communication following the transfer) was recorded with the remainder being recorded as missing data.

3.3.3 Missing data

In cases where medical notes were not obtainable at the first visit to the unit, a second attempt was made to retrieve them. In 15 cases it was not possible to obtain the notes at either visit so no data was collected from the patient notes. Available information from the discharge summary was recorded.

3.4 Data management

3.4.1 Data handling and entry

Data was abstracted from the notes onto the proforma (Appendix 13) at each participating hospital. A Microsoft® Access database was then created using the questionnaire format for data input, management and storage. Each proforma was single-entered into the database. To maintain a high level of confidentiality and data security personal information was kept in a separate database from clinical data and linked by unique study reference numbers. Once data collection was complete all identifiers were removed and destroyed and anonymous data identified only by study numbers was subsequently handled. Paper copies of data collection forms were stored in a locked filing cabinet, accessible only by members of the research team, within a locked office in the Department of Health Sciences. Data was entered into a secure Microsoft Access database. Single data entry was used due to time constraints. The University of Leicester Department of Health Sciences Infant Mortality and Morbidity Studies departmental data security protocol, and Information Technology policy, which are compliant with the Data Protection Act (1998), was adhered to at all times.

3.4.2 Data management

The data was subsequently exported to an IBM SPSS Statistics 22 database for analysis. The Microsoft Access database was compared with the SPSS data. The SPSS database was checked for errors and cleaned electronically by producing frequencies of responses to each item and looking for invalid

responses before analysing the data The SPSS programme automatically screened variables for blank entries to determine the proportion of missing data in each variable providing an indication of completeness i. e. proportion of data cells in each variable that contained valid cell values. When working with the data, fields with 'no' and 'yes' values were coded 0 and 1 respectively. Missing values were coded as '999'. Following data entry into the Microsoft Access database, data cleaning, manipulation and quality checking was undertaken in the Access datasheet view. The datasheet was manually cross checked against every form for accuracy.

3.5 Panel review

3.5.1 Case selection for discussion at panel meetings

A sample of sixteen infants was selected for presentation at panel. They were chosen to include a range of gestations, co-morbidities, neurological diagnoses and to reflect cases representing variation in clinical presentation, suspected risk factors for HIE, and co-morbidities in the cohort. They were selected to reflect cases with a variety of combinations of potential intrapartum or antepartum markers of hypoxia, non-HIE causes of NE, and varying numbers of features of NE. The sample was not representative of all of the neonatal units in the study. All cases in this sample were identified from one of the Trusts (comprising two neonatal units) participating in the study in order to facilitate presentation of the cases to the panel with minimal risk to data protection associated with transporting patient information between units.

3.5.2 Panel member recruitment

Twenty potential panel members were identified. They were neonatologists who had specialist knowledge and skills in the study area (HIE) (identified from publications and declared special interests) and came from a mixture of academic and clinical backgrounds within neonatology. No epidemiologists were identified. They were invited by letter and email to join the expert reference panel for the

study. Eight individuals (NM, AW, DF, DA, JB, SW, JC, DJ) agreed to join the group. They were asked to attend two face-to-face meetings to assist in the development of the epidemiological case definition for HIE. Five experts comprising one full time clinician and four academic clinicians were able to attend the first meeting (NM, AW, DF, DA, JB). Four experts comprising three full time clinicians and one part academic part clinician (AW, SW, JC, DJ) were able to attend the second meeting. The remaining experts were unable to attend the meetings due to conflicting obligations.

3.5.3 Pre-meeting preparation

Eight cases were prepared for discussion at each of the two panel meetings. Anonymised information regarding the antenatal history, labour and delivery and neonatal and infant course was collected for each of the eight cases and sent to the experts prior to each meeting.

3.5.4 First panel meeting

The first panel meeting took place on 10th February 2015 and was attended by five experts. A letter was circulated by email to all panel members prior to the face-to-face panel meeting, accompanied by a clear explanation of the objectives of the study and specific instructions for member participation. The data was presented by me and then clarified where necessary and discussed. Each expert was given a proforma and asked to rate each item according to its importance in the definition of moderate-severe HIE Experts were also given the opportunity to provide comments and suggest additional items that may not have been included when developing the initial list of items.

3.5.5 Feedback from first panel meeting

Following discussion with the panel members after the first meeting, a number of weaknesses in the process were highlighted, and suggestions were made for improvements in subsequent meetings. Verbal feedback from panel members

suggested that the diagnosis at various time points should be considered taking into account the further information available with time.

3.5.6 Second panel meeting

Three time points for which information could be provided were selected for evaluation of cases at the second panel meeting. These were six and 72 hours after delivery and two years of age. The rationale for these choices relates to times at which useful information was likely to become available to contribute to the diagnostic process within the two year follow up period of the study. Clinical assessment for therapeutic hypothermia is completed at up to six hours of age in most cases; most infants who have been identified as suitable for therapeutic hypothermia will complete 72 hours of therapeutic hypothermia and receive an assessment at this stage; and at two years of age further information about the clinical course and further investigations during infancy may be available from follow-up. Two years is also the time frame within which identification of long-term developmental problems such as cognitive impairment and cerebral palsy is first possible.

3.6 Classification of infants

Infants whose notes were reviewed were assigned a diagnosis by the panel of moderate-severe HIE at each time point (six hours, 72 hours and two years) if they fulfilled the criteria agreed by the panels.

3.7 Statistical Analyses

Data were entered and checked using Access (Microsoft) and analysed using SPSS version 22 (SPSS Inc., Chicago IL). Analysis was restricted to cases for whom data was available with total numbers indicated using N. Comparisons of prevalence of exposures in HIE versus non-HIE NE, for example using univariable analysis, were considered but were not thought to be appropriate.

3.8 Summary

In order to achieve the aim and objectives of the study, a literature review was conducted to identify features of HIE identified in the literature. A representative sample of infants was obtained from a range of nine neonatal units with a range of levels of care. Neonatal discharge summaries were reviewed to identify all infants with any one of the commonly used criteria for NE. For this population of infants with possible NE, data was collected regarding the antenatal, neonatal and early paediatric course. Experts were consulted at panel meetings to discuss the defining features of HIE and by extrapolating their advice the cohort was categorised into infants with and without HIE. The data was analysed in order to describe the features of infants with HIE, and to describe the aetiology. The existing diagnostic tools (TOBY) and screening tools (NNAP, TNS) for HIE were compared. There is no established gold standard for diagnosis of HIE; hence experts were invited to discuss the most well-established definition. The implications of replicating this work in a larger population was considered.

Chapter 4: Results

4.1 Introduction

The study aimed to explore the defining features of HIE for epidemiological use and the aetiology of HIE. In order to do this a representative population of infants in the East Midlands, Yorkshire and Humber regions with one or more signs of suspected neonatal encephalopathy was identified. Sixteen cases were selected by me to reflect the variation within the cohort with regard to presentation, course, and quality of information available. Expert panel meetings were held to discuss these selected cases. Following these discussions, reference standards for moderate to severe HIE at 12 hours of age, 72 hours of age and two years of age was developed. In this chapter the results of the various steps of the study are presented. (Please note that the pilot study results are presented within the methods section as their roles was in study design rather than data collection.)

4.2 Descriptive analysis of cohort of infants with one or more features of suspected encephalopathy

Neonatal discharge summaries were reviewed for infants of 35 or more weeks' gestation born at each of the eleven participating units between 1st July 2010 and 30th June 2011. 168 infants meeting the inclusion criteria (any one sign of neonatal encephalopathy (ie abnormal tone, conscious level, limb movements, or eye movements) within the first 96 hours) of life were identified. 153 data collection forms were completed from medical records (maternal and patient notes). Definitions of exposures of interest are given in Appendix 15. Forms were not completed for the remaining 15 infants as notes could not be obtained. Demographic information about these infants is presented in Table 4.1.

4.2.1 Demographic characteristics

The demographic characteristics of the infants identified at each unit and the missing infants is described in Table 4.1. Unit levels are described according to the BAPM classification of unit levels (Table 3.1). The number of infants identified varied considerably between units; this may reflect the variation in neonatal discharge summary data quality and completeness both within and between units. Of the included 153 infants, 88 (57.5%) were male and 104 (68.0%) were Caucasian. 71 (46%) were born at Neonatal Intensive Care units. 20 (13.1%) lived in areas with index of multiple deprivation score of 1 (maximal deprivation). The 15 infants for whom data collection was missing were comparable in most respects with similar mean maternal age, male sex, ethnicity, gestation and birthweight (Table 4.1); they had a shorter length of stay than the other infants which might indicate they were more well.

Table 4.1 Demographic characteristics of infants with one or more signs of suspected neonatal encephalopathy by unit level

	All	SCBUs	LNUs	NICUs	Missing
Number of infants identified	153	43	39	71	15
Maternal age mean (SD)	29.3 (7.2)	28.0 (6.8)	30.0 (8.3)	29.7 (6.7)	27.2 (8.1)
Male sex n (%)	88 (57.5)	23 (53.5)	23 (59.0)	42 (59.2)	9 (60.0)
Ethnicity Caucasian n (%) Asian n (%) African n (%)	 104 (68.0) 36 (23.5) 13 (8.5)	 28 (65.1) 7 (16.3) 8 (18.6)	 26 (66.7) 11 (28.2) 2 (5.1)	 50 (70.4) 18 (25.4) 3 (4.2)	 11 (73.3) 3 (20.0) 1 (6.7)
Gestation (weeks) (mean; SD)	39.2 (1.9)	39.2 (1.8)	39.0 (1.7)	39.2 (2.1)	39.7 (1.5)
Birthweight (kg) (median;IQR)	3.22 (2.72-3.65)	3.3 (2.75-3.68)	3.22 (2.69-3.47)	3.20 (2.7-3.8)	3.56 (3.07-3.95)
Admission length (days) (median, IQR)	7.2 (2.0-15.0)	1.1 (0.3-7.2)	7.3 (4.1-16.0)	8.4 (3.5-16.0)	3.9 (1.7-10.0)

Table 4.1 Demographic characteristics of infants with one or more signs of suspected neonatal encephalopathy by unit level (continued)

	All	SCBUs	LNUs	NICUs	Missing
Index of multiple deprivation (IMD) quintile group n (%)					
1	20 (13.1)	3 (7.0)	8 (20.5)	9 (12.7)	1 (6.7)
2	17 (11.1)	5 (11.6)	2 (5.1)	10 (14.1)	1 (6.7)
3	25 (16.3)	9 (20.9)	6 (15.4)	10 (14.1)	2 (13.3)
4	32 (20.9)	8 (18.6)	7 (17.9)	17 (23.9)	4 (26.7)
5	57 (37.3)	18 (41.9)	16 (35.9)	25 (35.2)	7 (46.7)

4.2.2 Pregnancy

73 (47.7%) of mothers were primiparous . 8.3% of mothers had a history of stillbirth/medical termination/ miscarriage/preterm birth. 114 (74.5%) of mothers had taken folic acid in pregnancy. 64 (40.5%) had taken iron supplementation in pregnancy.

Table 4.2: Pregnancy of infants with one or more signs of suspected neonatal encephalopathy by unit level

	All N=153	SCBUs N=43	LNUs N=39	NICUs N=71
Obstetric history				
Primiparity (%)	125 (81.7)	31 (72.1)	36 (92.3)	6 (8.5)
History of stillbirth	1 (0.7)	1 (2.3)	0	0
Medical termination of Pregnancy	4 (2.6)	2 (4.6)	2 (5.1)	0
Miscarriage (%)	4 (2.6)	0	0	4 (5.6)
Preterm birth (%)	4 (2.6)	2 (4.6)	2 (5.1)	0
Maternal folic acid in pregnancy (%)	114 (74.5)	31 (72.1)	27 (69.2)	56 (78.9)
Maternal iron in pregnancy (%)	62 (40.5)	6 (14.0)	0	56 (78.9)
Maternal medication in pregnancy other than iron or folic acid (%)	18 (12.6)	10 (21.7)	0	8 (11.2)

Table 4.2: Pregnancy of infants with one or more signs of suspected neonatal encephalopathy by unit level (continued)

	All	SCBUs	LNUs	NICUs
Fertility Treatment for this pregnancy (%)	1 (0.7)	0	0	1 (1.4)
Maternal tobacco use (%)	17 (11.9)	4 (9.3)	5 (12.8)	8 (11.3)
Maternal alcohol use (%)	11 (7.7)	4 (9.3)	2 (5.1)	5 (7.0)
Maternal recreational drug use (%)	15 (10.5)	4 (9.3)	6 (15.4)	5 (7.0)

4.2.3 Maternal illness

The commonest maternal illness prior to pregnancy was hypothyroidism with 4 (2.6%) affected. 27 mothers (17.6%) had a family history of illness; however only 1 (0.7%) had a family history of neurological illness. The commonest illness during pregnancy was anaemia, occurring in 35 (22.9%), followed by infection occurring in 10 (6.5%) of infants. 149 (97.4%) underwent a detailed antenatal ultrasound.

Table 4.3 Maternal illness of infants with one or more signs of suspected neonatal encephalopathy by unit level

	All N=153	SCBUs N=43	LNUs N=39	NICUs N=71
Family history				
Family history of congenital abnormalities (%)	7 (4.6)	3 (7.0)	0	4 (5.6)
Family history of neurological problems (%)	1 (0.7)	1 (2.3)	0	0
Family history of multiple births (%)	5 (3.3)	4 (9.3)	0	1 (1.4)
Family history of hypertension (%)	7 (4.6)	4 (9.3)	0	3 (4.2)
Family history of diabetes mellitus (%)	7 (4.6)	3 (7.0)	2 (5.1)	2 (2.8)

Table 4.3 Maternal illness of infants with one or more signs of suspected neonatal encephalopathy by unit level (continued)

	All N=153	SCBUs N=43	LNUs N=39	NICUs N=71
Maternal medical history				
Maternal gestational diabetes in previous pregnancy (%)	10 (6.5)	1 (2.3)	4 (10.3)	5(7.0)
Maternal epilepsy (%)	2 (1.3)	0	2 (5.1)	0
Maternal hypothyroidism (%)	4 (2.6)	2 (4.7)	0	2 (2.8)
Maternal neurological disorder (%)	4 (2.6)	0	4 (10.3)	0
Maternal illness during pregnancy				
Maternal infection during pregnancy (%)	10 (6.5)	2 (4.7)	0	8 (11.3)
Maternal group B streptococcus colonisation (%)	11 (7.2)	2 (4.6)	3 (7.7)	6 (8.5)
Maternal anaemia (%)	35 (22.8)	5 (11.6)	14 (35.9)	16 (22.5)
Maternal antepartum hemorrhage (%)	15 (9.8)	2 (4.7)	6 (15.4)	7 (9.9)
Maternal gestational diabetes mellitus (%)	7 (4.6)	3 (7.0)	0	4 (5.6)
Maternal gestational proteinuria (%)	8 (5.2)	4 (9.3)	0	4 (5.6)
Maternal pre-eclamptic toxaemia (%)	7 (4.6)	3 (7.0)	0	4 (5.6)
Antenatal investigation				
Detailed antenatal USS done (%)	149 (97.4)	41 (95.3)	37 (94.9)	71 (100)
Abnormal antenatal USS (%)	23 (15.0))	7 (16.3)	3 (7.7)	13(18.3)
Extra antenatal USS (%)	25 (16.3)	8 (18.6)	3 (7.7)	14 (19.7)

4.2.4 Labour and delivery

111 (79.0%) of mothers had cardiotocography monitoring. 144 (94.1%) infants were cephalic presentation.

Table 4.4 Labour and delivery of infants with one or more signs of suspected neonatal encephalopathy by unit level

	All N=153	SCBUs N=43	LNUs N=39	NICUs N=71
Monitoring during labour				
Cardiotocogram done	121 (79.1)	31 (72.1)	32 (82.1)	58 (81.7)
Foetal scalp electrode performed	2 (1.3)	1 (2.3)	0	1 (1.4)
Presentation				
Cephalic presentation	144 (94.1)	39 (90.7)	38 (97.4)	67 (94.4)
Malpresentation	10 (6.5)	4(9.3)	1 (2.6)	5 (7.0)
Delivery				
Spontaneous vaginal delivery	66 (43.1)	17 (39.5)	21 (53.8)	28 (39.4)
Instrumental delivery (%)	34 (22.1)	10 (23.2)	8 (20.5)	16 (22.5)
Elective Caesarean (%)	18 (11.8)	2 (4.7)	3 (7.7)	13 (18.3)
Emergency Caesarian in labour(%)	31 (20.3)	12 (27.9)	6 (15.4)	13 (18.3)
Emergency Caesarian not in labour (%)	2 (1.3)	0	0	2 (2.8)
Condition at delivery				
Apgar at 5 minutes <6	51 (33.3)	13 (30.2)	11 (28.2)	27 (38.0)
Apgar at 10 minutes <6	5 (3.3)	2 (2.8)	1 (1.4)	2 (2.8)
Need for ventilatory resuscitation	83 (54.2)	23 (53.5)	19 (48.7)	41 (57.7)
Need for ventilatory resuscitation at 5 minutes	51 (33.3)	13 (30.2)	11 (28.2)	27 (38.0)
Need for ventilatory resuscitation at 10 minutes	41 (26.8)	11 (25.6)	8 (20.5)	22 (31.0)

Table 4.4 Labour and delivery of infants with one or more signs of suspected neonatal encephalopathy by unit level (continued)

	All N=153	SCBUs N=43	LNUs N=39	NICUs N=71
Anaesthesia				
Epidural anaesthesia during delivery (%)	20 (13.1)	7 (16.3)	3 (7.7)	10 (14.1)
Spinal regional anaesthesia during delivery (%)	34 (22.2)	11 (25.6)	6 (15.4)	17(23.9)
General anaesthesia during delivery (%)	11 (7.2)	0	1 (2.6)	10(14.1)
Opiate during delivery	1 (0.7)	1 (2.3)	0	0
Spinal regional anaesthesia during delivery (%)	34 (22.2)	11 (25.6)	6 (15.4)	17(23.9)
General anaesthesia during delivery (%)	11 (7.2)	0	1 (2.6)	10(14.1)
Opiate during delivery	1 (0.7)	1 (2.3)	0	0

4.2.5 Neonatal features

The commonest presenting symptoms were abnormal tone during the first 96 hours in 106 (69.3%) and abnormal consciousness in 106 (69.3%) of infants. The use of investigations was very variable. aEEG was performed in 101 (66.0%) of infants. Raw aEEG data was available in only 9 (5.9%) of infants.

Table 4.5: Neonatal features of infants with one or more signs of suspected neonatal encephalopathy by unit level

	All N=153	SCBUs N=43	LNUs N=39	NICUs N=71
Presenting symptom				
Abnormal consciousness during first 96 hours of life (%)	106 (68.9)	25 (58.1)	27 (69.2)	54(76.1)
Abnormal tone during first 96 hours of life (%)	106 (68.9)	31 (72.1)	21 (53.8)	54(76.1)
Abnormal movements during first 96hours of life (%)	34 (22.2)	12 (27.9)	10 (25.6)	12 (16.9)
Abnormal eye movements during first 96h of life (%)	2 (1.3)	1 (2.3)	0	1 (1.4)
Neurophysiology				
aEEG done (%)	101 (66.0)	29 (67.4)	29 (74.4)	43 (60.6)
Raw aEEG available (%)	9 (5.9)	0	0	9 (12.7)
EEG performed (%)	57 (37.3)	15 (34.9)	12 (30.2)	30 (42.3)
Neuroimaging				
Cranial USS performed (%)	105 (68.6)	28 (65.1)	27 (69.2)	50 (70.4)
Resistive index measured (%)	15 (9.8)	3 (7.0)	3 (7.7)	9 (12.7)
Early MRI (%)	18 (11.8)	1 (2.3)	5 (12.8)	12 (16.9)
Late MRI (%)	35 (22.9)	5 (11.6)	9 (23.1)	21 (29.6)

4.3 Panel review process

4.3.1 Selection of panel cases

Sixteen cases were selected by me for discussion at panel meetings to reflect the variation within the cohort as above. These cases were chosen to reflect the variation within the cohort and included cases with typical features of HIE, cases with uncertainty with regard to markers of hypoxia, and cases with uncertainty with regard to signs of encephalopathy.

Table 4.6: Brief clinical summary of cases discussed at panel meetings

Case	Brief clinical summary
1	Poor condition at delivery, ventilated, transferred to cooling centre, not cooled
2	Hypoglycaemia, stroke
3	Group B streptococcus meningitis
4	Poor condition at birth, seizures
5	Poor condition at birth, quick recovery, hypoglycaemia
6	Prolonged hypoglycaemia, seizures
7	Poor condition at birth, seizures, received cooling
8	Poor condition at birth, syndromic
9	Poor condition at birth, transferred for cooling
10	Seizures associated with hypoglycaemia, polycythaemia and necrotising enterocolitis
11	Uterine rupture followed by reduced consciousness and hypotonia, seizures, burst suppression, MRI changes.
12	Initial hypotonia, reduced consciousness, diagnosed at 6 months with mitochondrial disease
13	Chromosomal deletion, seizures, infant epilepsy
14	Poor condition at birth, hypothyroid, MRI changes of chronic hypoxia
15	Skull fracture, intracranial haemorrhage, poor condition at birth, seizures
16	Foetal distress, seizures

The eight cases discussed at the first panel meeting are labelled cases 1-8. The eight cases discussed at the second panel meeting are labelled 9-16.

4.3.2 Components of panel discussion

4.3.2.1 Review of clinical diagnoses

The panel agreed that they find the existing TOBY definition of HIE a definition with good clinical utility. Over the course of this review process the panel noted a number of instances of inadequate neurological examination, aEEG of suboptimal quality, and incorrect aEEG interpretation. Overall the quality of neurological examination and interpretation of aEEG was poor and this affected the ability to diagnose moderate-severe HIE The diagnosis of moderate-severe HIE might be improved by measures to improve these, for example systematic neurological examination using a published tool. aEEG interpretation might be improved by mandatory aEEG training for clinicians involved in assessing infants for moderate-severe HIE, particularly those working in tertiary centres offering and retrieving infants for therapeutic hypothermia. The emerging use of telemedicine might further improve assessment of potential infants with HIE born at level 1 or 2 units by level 3 unit clinicians. The panel agreed that when the TOBY definition is used by junior clinicians and/or in units with limited access to specialist equipment and/or advice, there may be scope for misinterpretation leading to overdiagnosis of HIE.

Table 4.7: Summary of contemporaneous clinical evaluation of infants

Panel case	Cord gas obtained	Day 1 Neuro-logical exam-ination perform-ed	Day 1 Neuro-logical exam-ination perform-ed by doctor above ST2	Day 1 neuro-logical exam-ination perform-ed prior to sedation	Day 1 Neuro-logical exam-ination perform-ed using assess-ment tool	aEEG done	Good quality aEEG done	MRI perform-ed	DWI perform-ed	Develop-ment formal assess-ment at two years
1	No	Yes	No	No	NA	No	NA	No	No	None
2	Yes	Yes	Yes	NA	No	Yes	Yes	Yes	Yes	SGS
3	Yes	Yes	No	NA	No	Yes	No	Yes	Yes	SGS
4	Yes	Yes	No	NA	No	Yes	No	Yes	Yes	SGS
5	Yes	Yes	No	NA	No	No	NA	Yes	Yes	SGS
6	Yes	Yes	No	NA	No	No	NA	Yes	Yes	SGS
7	Yes	Yes	No	No	No	Yes	No	Yes	Yes	SGS
8	Yes	Yes	No	NA	NA	Yes	Yes	No	No	No
9	No	No	No	No	No	Yes	No	No	NA	SGS
10	Yes	No	No	NA	No	No	NA	Yes	Yes	SGS
11	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Died
12	Yes	No	NA	NA	NA	Yes	No	No	No	Died
13	Yes	No	NA	NA	No	No	Yes	No	No	No
14	Yes	No	NA	NA	No	No	NA	Yes	Yes	None
15	Yes	Yes	Yes	Yes	No	Yes	Yes	No	No	SGS
16	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	SGS

4.3.2.2 Scope of definition

The panel agreed that the agreed definition should be used as a reference standard in the epidemiological context of this study to identify cases of NE and HIE. As HIE is a heterogenous condition and moderate-severe HIE is often grouped together it is appropriate to seek to define moderate-severe HIE for this purpose. Criteria should be applied prospectively using raw data rather than retrospectively in order to avoid the effects of observer bias. This applies particularly to the CTG, neurological examination, aEEG, and MRI findings.

4.3.2.3 Time points of definition

The rigour of the diagnosis increases with time as more diagnostic information becomes available from both the infant's course as well as the results of further neurological, metabolic and other investigations.

4.3.2.4 Components of definition

For each case the evidence of fetal hypoxia, evidence of encephalopathy, refuting factors for HIE and any alternative causes of NE identified were discussed. This incorporated both clinical features (Table 4.8) and investigation results (Table 4.9).

Table 4.8 Summary of clinical features of panel cases

Panel case	Evidence of fetal hypoxia	Evidence of encephalopathy	Refuting factors for moderate-severe HIE	Non HIE cause of NE identified on neonatal or paediatric investigations
1	Meconium staining, poor condition at delivery, raised creatinine, Apgar 3 at 5 minutes, small for gestational age 2.9kg, umbilical arterial pH 6.9	Ventilated at delivery for poor respiratory effort	No clearly documented encephalopathy	None
2	CTG decelerations, meconium, small for gestational age 2.77kg, umbilical arterial pH 7.05	Seizures, abnormal EEG background	Neurological features better explained by hypoglycaemia	Hypoglycaemic stroke
3	CTG suspicious, umbilical arterial pH 7.05	Seizures	Neurological features better explained by meningitis	Group B strep meningitis
4	Reduced fetal movements, pathological CTG, poor condition at birth, small for gestational age 2.975kg, umbilical arterial pH 6.83	Ventilated at delivery for poor respiratory effort,	No	No
5	Reduced fetal movements, pathological CTG, poor condition at birth, umbilical arterial pH 7.22, IUGR 2246g	Hypotonia, unresponsive	Neurological features better explained by hypoglycaemia	Hypoglycaemia due to hyperinsulinism
6	CTG decelerations, meconium staining, poor condition at birth, small for gestational age 2.82kg, umbilical arterial pH 7.21	Seizures	Neurological features better explained by hypoglycaemia	Prolonged hypoglycaemia
7	Decreased fetal movements, abnormal CTG, meconium staining, poor condition at delivery, Apgar 6^5, small for gestational age 2.89kg, umbilical arterial pH 6.90	Seizures	Neurological features better explained by effect of muscle relaxant and sedation use, infarct, initial hypoglycaemia	Muscle relaxant and sedation use, infarct, initial hypoglycaemia
8	Fetal bradycardia, IUGR 1.9kg, poor condition at birth, umbilical arterial pH 6.67	Initial hypotonia and respiratory failure	Neurological features better explained by syndrome associated with central hypotonia	No
9	Fetal bradycardia, poor condition at birth, cord acidemia pH 6.6	Hypertonia, irritability, ventilated at birth for poor respiratory effort	Insufficient information to determine condition prior to ventilation and sedation	No
10	Cord pH 7.23, ALT-anaemia, thrombocytopenia	Seizures	Neurological features better explained by hypoglycaemic stroke	Hypoglycaemic stroke
11	Uterine rupture, poor condition at birth, cord acidemia pH 6.76, Apgar 4^5	Unresponsive to pain, hypotonia, seizures, ventilatory failure	aEEG difficult to interpret	Neuronal migration disorder
12	Small for gestational age 2.6kg, meconium stained liquor, umbilical arterial pH 7.11, poor condition at birth	Hypertonia, poor suck, seizures	Neurological features better explained by Pearson syndrome	Mitochondrial disorder (Pearson syndrome)
13	Delayed extraction, cord acidemia, small for gestational age 2.66kg	Seizures	Neurological features better explained by chromosomal deletion	Chromosomal deletion
14	Poor condition at birth, renal impairment	Abnormal tone and conscious level	Short duration of encephalopathy	Hypothyroidism
15	Poor condition at birth	Seizures, hypertonia, opisthotonus	Neurological features better explained by intracranial hemorrhage	Acute hemorrhagic stroke
16	Reduced fetal movements, CTG reduced variability, IUGR 2.1kg, Poor condition at birth, umbilical arterial pH 7.06, respiratory failure, thrombocytopenia	Seizures, hypotonia, poor respiratory effort	No	No

Table 4.9: Summary of investigations for encephalopathy of panel cases

Panel case	aEEG	EEG	MRI	Condition at 2 years
1	Not done	Not done-	Subdural haematoma	Normal development
2	Seizures	Epileptiform activity	Parieto-occipital infarct Cerebellar microhemorrhages	Speech delay
3	Electroclinical seizures	Frequent epileptiform activity	Diffuse ischaemia	Speech, vision, fine motor delay
4	Moderately abnormal	Interictal epileptiform activity	Thalamus changes	Unknown
5	Not done	Mild dysfunction	Petechial haemorrhages in caudate and white matter	Normal development
6	Not done	Cerebral dysfunction	Extensive oedema and cortical highlighting both parieto-occipital and left Fronto-parietal lobes.	Global developmental delay
7	Seizures	Interictal epileptiform activity	Regions of periventricular acute infarction, occipital microhemorrhages	Normal
8	Normal background	Not done	Not done	Global delay
9	Poor quality	Sharp activity	Not done	Normal development
10	Not done	Background discontinuous, interictal epileptiform activity	Occipital infarct	Epilepsy, normal development
11	Moderate-severe encephalopathy	Not done	Large posterior interhemispheric arachnoid cyst, subependymal heterotopia	Died in neonatal period
12	Poor quality	Normal	Normal	Died in infancy
13	Not done	Normal	Not done	Global delay
14	Not done	Not done	Diffuse cortical ischaemic changes	Unknown
15	Seizures	Not done	Multiple intracranial haemorrhages with cerebral oedema and midline shift and uncal herniation	Normal
16	Electrical seizures	Normal background with excess left sided sharp Activity	Normal	Normal

4.4 Development of reference standard by consensus

The panel discussed each of the sixteen cases and tried to reach a consensus regarding a diagnosis of NE and HIE.

Table 4.10: Panel consensus regarding clinical diagnosis of moderate-severe NE and HIE

Panel case	Consensus moderate –severe HIE at six h (%)	Consensus moderate – severe HIE at 72 h (%)	Consensus moderate – severe HIE at two years (%)	Consensus non – HIE NE at two years (%)
1	Not applicable	Not applicable	No (100)	No (100)
2	Not applicable	Not applicable	No (100)	Yes (100)
3	Not applicable	Not applicable	No (100)	Yes (100)
4	Not applicable	Not applicable	Yes (100)	No (100)
5	Not applicable	Not applicable	No (100)	Yes (100)
6	Not applicable	Not applicable	No (100)	Yes (100)
7	Not applicable	Not applicable	No (100)	No (100)
8	Not applicable	Not applicable	No (100)	No (100)
9	Insufficient Information (100)	Insufficient information (100)	Insufficient information (100)	No (100)
10	Insufficient information (75) No (25)	Insufficient information (75) No (25)	Insufficient information (75) No (25)	No (100)
11	Yes (100)	Yes (100)	Yes (100)	No (100)
12	Insufficient information (100)	No (100)	No (100)	Yes (100)
13	No (100)	No (100)	No (100)	No (100)
14	No (100)	No (100)	No (100)	No (100)
15	No (100)	No (100)	No (100)	Yes (100)
16	No (100)	No (100)	No (100)	No (100)
Total N Con-sensus (%)	8 No (53.1)	8 No(65.6)	16 No (76.6)	16 No (62.5)

The conclusions of the panel meetings were used to inform the development of reference standards for the study. The neurological assessment should be interpreted for signs of HIE. The panel identified some caveats in its application particularly retrospectively. They agreed that infants with transient disturbance of conscious level and tone who recover within the first hour of life should not be classified as encephalopathic. Although the definitions of moderate to severe encephalopathy often include infants with seizures, infants presenting with seizures alone can be unwell due to a number of causes and do not behave similarly to infants presenting with abnormal tone and conscious level and hence should be studied separately.

In those cases where there is a neurological diagnosis other than HIE and findings are consistent with NE due to this diagnosis, it is unlikely that the infant

also had HIE, unless there is very strong supporting evidence for hypoxia ischaemia such as a sentinel event. Markers of hypoxia and ischaemia should be sought; markers of particular value include Pregnancy history (eg reduced fetal movements), Labour and delivery history (eg passage of meconium), Condition at birth (particularly apnoeic, floppy), growth restriction, Cord or early neonatal acidemia, Resuscitation (particularly ongoing need for resuscitation at 10 minutes), and MRI (particularly basal ganglia thalamus distribution changes on early diffusion weighted imaging).

Box 4.1: Reference standard for moderate-severe HIE at 12 hours

- Fetal hypoxia markers
- Clinical features of neonatal encephalopathy – abnormal condition at delivery, tone and conscious level persisting for at least one hour after delivery
- aEEG features of neonatal encephalopathy supporting evidence from MRI if done
- consider whether alternative diagnosis can explain presentation

Box 4.2: Reference standard for moderate-severe HIE at three days

- Clinical features of neonatal encephalopathy – abnormal condition at delivery, tone and conscious level persisting for at least one hour after delivery
- aEEG features of neonatal encephalopathy supporting evidence from MRI if done
- consider whether alternative cause of NE can explain presentation

Box 4.3: Reference standard for moderate-severe HIE at two years

- Fetal hypoxia markers
- Clinical features of neonatal encephalopathy – abnormal condition at delivery, tone and conscious level persisting for at least one hour after delivery
- aEEG features of neonatal encephalopathy
- Corroborating information from placental histology, MRI, post mortem if done
- Lack of alternative cause of neonatal encephalopathy from further investigations

4.5 Application of reference standard to identify infants with NE within cohort

The reference standard for moderate – severe NE was applied to the study population based on all of the information available at two years of age. Out of the 153 infants with one or more signs of suspected neonatal encephalopathy, following application of the reference standard, 54 (35.3%) were identified as having moderate-severe NE. The remaining infants with one or more signs of suspected NE had either no evidence of NE (63.4%) or evidence of hypoxic-ischaemic encephalopathy due to a post- natal insult (1.3%). In the infants with no evidence of NE the following underlying conditions were identified - neonatal abstinence syndrome, genetic syndromes, mitochondrial disorder, stroke, intracranial abscess, neuronal migration disorder, meningomyelocoele, hypoglycaemia and meningitis. No cases of mild HIE were identified.

Table 4.11 : Presence of moderate-severe neonatal encephalopathy in study cohort

	N	%
Evidence of neonatal encephalopathy	54	35.3
• Hypotonia and reduced conscious level persisting beyond delivery room during first 96 hours of life	35	24.8
• Seizures during first 96 hours of life	19	12.4
Evidence of hypoxic ischaemic encephalopathy due to post natal insult	3	1.3
No evidence of neonatal encephalopathy	96	63.4
• Hypotonia and reduced consciousness limited to first hour of life	54	35.3
• Neonatal abstinence syndrome	18	11.8
• Hypotonia relating to myelomeningocele	9	5.9
• Hypotonia relating to underlying syndrome	14	9.1
• Hypotonia relating to neuromuscular condition	1	1.0

4.6 Descriptive analysis of infants with HIE and non-HIE NE

As described in the previous section, the expert criteria for moderate to severe HIE above (box 4.3) were applied at the three time points as had been agreed by the panel : 6 hours of life, 72 hours of life, and two years of life (table 4.12). Out of the 54 infants with moderate-severe NE identified, following application of the reference standard, 29 (53.7%) infants were identified as meeting the expert criteria. In 17 infants there was insufficient information available to determine the presence of NE at 6 hours and this was due to insufficient information from documented neurological examination or aEEG (poor quality or not done). The diagnosis in these 17 infants was established by 72 hours. In most infants there was no change between this diagnosis at 72 hours and the diagnosis at the end of the two year period studied. However in one infant the diagnosis of HIE was made based on the information available at two years but not at 72 hours. Further descriptive analysis was undertaken on the 29 infants meeting the reference standard for moderate-severe HIE based on the information available at two years.

Table 4.12 Diagnosis of infants meeting expert criteria for NE at two years at earlier time points

	Information available at six hours of life N=54	Information available at 72 hours of life N=54	Information available at two years of life N=54
NE based on expert Criteria(%)	38 (70.4)	54 (100)	54 (100)
HIE based on expert criteria at 2 years (%)	26 (48.2)	28 (51.9)	29 (53.7)
Insufficient information to determine presence of NE (%)	17 (31.5)	0	0
Insufficient information to determine presence of HIE (%)	6 (11.1)	0	0

4.6.1 Demographic characteristics of infants with NE

Of the 153 infants in the study, 29 infants met the reference standard criteria for moderate to severe HIE based on the information available at two years of age. Of the 29 infants classified as moderate to severe HIE, 18 (62.1%) were male. 8 (27.6%) were from postcodes with index of multiple deprivation of the highest quintile (ie maximal deprivation). 21 (72.4%) were of European ethnicity, with 6 (21.4%) of Asian ethnicity and 2 (7.1%) of African ethnicity. No mothers had hypertension, hyperthyroidism or hypothyroidism. More mothers with non-HIE NE were unemployed (64.0%) than in the HIE subgroup (48.3%).

Table 4.13: Demographic characteristics of infants meeting expert clinical criteria for moderate to severe HIE based on information available at two years.

	Infants with moderate- severe HIE according to expert criteria at two years (%)	Infants with NE without HIE	All infants with NE
Total number	29	25	54
Sex male	18 (62.1)	13 (52.0)	31 (57.4)
IMD quintile			
1	4 (13.8)	3 (12.0)	7 (13.0)
2	5 (17.2)	1 (4.0)	6 (11.1)
3	4 (13.8)	4 (16.0)	8 (14.8)
4	7 (24.1)	7 (28.0)	14 (25.9)
5	8 (27.6)	10 (40.0)	18 (33.3)
Ethnicity			
European	21 (72.4)	18 (72.0)	39 (72.2)
Asian	6 (20.7)	3 (12.0)	9 (16.7)
African	2 (6.9)	4 (16.0)	6 (11.1)
Mother unemployed	14 (48.3)	16 (64.0)	31 (57.4)

4.7 Comparative analysis of infants with HIE and non-HIE NE

The 29 infants with HIE and 25 infants with non-HIE NE were compared with regard to a number of potential maternal, antenatal, neonatal and infant risk factors. Due to the small sample obtained, the study did not achieve the predicted power of 0.8 for binomial regression. Binomial regression analysis to compare the two groups was therefore not undertaken.

4.7.1 Clinical features

4.7.1.1 Condition at birth

Infants with HIE were more likely to have an Apgar score of less than 6 at five minutes, need for any ventilatory resuscitation, need for ventilatory resuscitation at 5 minutes and need for ventilatory resuscitation at 10 minutes.

Table 4.14 Comparison of condition at birth between infants with HIE and non-HIE NE

Condition at birth	Infants with moderate-severe HIE according to expert criteria at two years (%). N=29	Infants with NE without HIE (%) N=25	All infants with NE (%) N=54
Apgar at 5 minutes less than 6	12 (41.4)	1 (4.0)	13 (24.1)
Apgar at 10 minutes less than 6	3 (10.3)	1 (4.0)	4 (7.5)
Need for any ventilatory resuscitation	26 (89.7)	2 (8.0)	28 (51.9)
Need for ventilatory resuscitation at 5 minutes	22 (75.9)	2 (8.0)	24 (44.4)
Need for ventilatory resuscitation at 10 minutes	14 (48.3)	2 (8.0)	16 (29.6)

4.7.1.2 Presenting features

Out of the 29 infants with HIE, 29 (100%) had abnormal (low) conscious level at presentation. 28 (96.6%) had abnormal (low) tone. Nine (31.0%) had abnormal

limb movements; all of which were described as seizures. None had abnormal eye movements at presentation. In comparison, infants with non-HIE NE less commonly presented with abnormal conscious level (11 infants or 44.0%) or abnormal tone (10 infants or 40.0%) and more often presented with abnormal limb movements (19 infants or 76.0%).

Table 4.15: Comparison of presenting features between infants with HIE and non-HIE NE

Symptoms at presentation	Infants with moderate-severe HIE according to expert criteria at two years (%) N=29	Infants with NE without HIE (%) N=25	All infants with NE (%) N=54
Abnormal conscious level	29 (100)	11 (44.0)	40 (74.1)
Abnormal tone	28 (96.6)	10 (40.0)	38 (70.4)
Abnormal limb movements	9 (31.0)	19 (76.0)	28 (51.9)
Abnormal eye movements	0	2 (8.0)	2 (3.7)

4.7.1.3 Neurophysiological investigations

All infants underwent aEEG. aEEG reports and raw aEEG where accessible showed moderate encephalopathy in 13 infants (46.4%) and moderate encephalopathy in eight infants (28.6%), with electrical seizures in seven (25.0%). EEG was performed in 16 (55.2%) infants, usually at two-three days of age. Three infants had EEG evidence of encephalopathy (10.7%).

Table 4.16 Comparison of neurophysiological investigations between infants with HIE and non- HIE NE

Investigation	Infants with moderate-severe HIE according to expert criteria at two years (%) N=29	Infants with NE without HIE (%) N=25	All infants with NE (%) N=54
aEEG done	29 (100)	23 (92.0)	52 (96.2)
Moderate/severe encephalopathy on aEEG	29 (100)	18 (72.0)	47 (87.0)
Electrical seizures on D1-D4 aEEG	9 (31.0)	7 (28.0)	16 (29.6)
EEG done	16 (55.2)	11 (44.0)	27 (50.0)
EEG evidence of encephalopathy	0	1 (4.0)	1 (1.9)

4.7.1.4 Neuroimaging

All infants underwent cranial ultrasound imaging. Cerebral oedema was identified in two (7.1%) patients on ultrasound. A low resistive index was identified in 14 (48.3%) infants. MRI was performed in 18 (64.3%) of infants. On MRI basal ganglia changes were identified in 6 (20.7%). The remaining 12 infants had MRI reported as normal. No infants were identified with cortical ischaemic changes.

Table 4.17: Comparison of imaging between infants with HIE and non-HIE NE

Imaging	Infants with moderate-severe HIE according to expert criteria at two years (%) N=29	Infants with NE without HIE (%) N=25	All infants with NE (%) N=54
Cranial USS done by either neonatologist or radiologist	29 (100)	24 (96.0)	53 (98.1)
Resistive index <0.55	14 (48.3)	1 (4.0)	15 (27.8)
Early MRI performed	7 (24.1)	5 (20.0)	12 (22.2)
Late MRI performed	21 (72.4)	5 (20.0)	26 (48.1)
MRI basal ganglia changes (%)	6 (20.7)	2 (8.0)	8 (14.8)
MRI cortical ischaemic changes (%)	0	2 (8.0)	2 (3.8)

4.7.1.5 Management

Therapeutic hypothermia was administered in 27 out of the 29 infants (93.1%). In all of these infants it was given for 72 hours. Passive therapeutic hypothermia was given prior to active TH in 24 (82.8%) of infants. 4 (14.3%) infants were transferred from a non-cooling centre hospital to another cooling centre hospital. Two infants with non-HIE NE received TH. This may be due to the clinical picture at the time being suggestive of HIE and this being refuted by subsequent progress.

Table 4.18: Comparison of management between infants with HIE and non-HIE NE

Management	Number of infants with moderate-severe HIE according to expert criteria at two years (%) N=29	Infants with non-HIE NE (%) N=25	All infants with NE (%) N=54
Sedation drugs in first 4 days	7 (24.1)	1 (4.0)	8 (14.8)
Muscle relaxant drugs in first 4 days	3 (10.3)	4 (16.0)	7 (13.0)
Passive therapeutic hypothermia	24 (82.8)	2 (8.0)	26 (48.1)
Active therapeutic hypothermia of any duration	27 (93.1)	1 (4.0)	28 (51.9)
Active therapeutic hypothermia for seventy two hours	27 (93.1)	1 (4.0)	28 (51.9)
Transfer for therapeutic hypothermia	4 (14.3)	2 (8.0)	6 (11.1)

4.7.1.6 Infancy

There was variable documentation of the course of the infants at two years of age. Two year neonatology follow up clinic documentation was obtained in 19 infants (35.2%) of which neurodevelopmental clinic documentation was obtained in 12 infants (22.2%). In comparison with infants with moderate-severe HIE, infants with non-HIE NE more often developed epilepsy (16.0% compared to 3.4%), moderate-severe developmental delay (32.0% compared to 6.9%), and cerebral palsy (16.0% compared to 13.8%). Post mortem examination following HIE was carried out in 4 (13.8%) of cases,

Table 4.19: Comparison of course during infancy between infants with HIE and non-HIE NE

	Number of infants with moderate-severe HIE according to expert criteria at two years (%) N=29	Infants with non-HIE NE (%) N=25	All infants with NE (%) N=54
Epilepsy	1 (3.4)	4 (16.0)	5 (9.2)
Cerebral palsy	4 (13.8)	4 (16.0)	8 (14.8)
Moderate/severe developmental delay	2 (6.9)	8 (32.0)	10 (18.5)
Death in neonatal period	5 (17.2)	0	5 (9.2)
Death before the age of 2	5 (17.2)	1(4.0)	6 (11.1)
Coroners post mortem performed	4 (13.8)	0	4 (7.4)
Post mortem consistent with HIE	4 (13.8)	0	4 (7.4)

4.7.2 Possible aetiological factors

4.7.2.1 Maternal factors

More mothers of infants with HIE (96.0%) were multiparous compared to mothers of infants with non-HIE NE (72.4%). More mothers reported tobacco and recreational drug use in the non-HIE NE group than the HIE group; however the numbers were small. Infants with HIE were less likely to have a family history of illness (3.4% compared to 32.0%). Mothers of infants with HIE were more likely to have pre-existing illness (13.8% compared to 4.0%.), infection (27.6%) and anaemia (20.7%).

Table 4.20 Comparison of maternal factors between infants with HIE and non-HIE NE

	Infants with moderate-severe HIE according to expert criteria at two years (%) N=29	Infants with NE without HIE (%) N=25	All infants with NE (%) N=54
Obstetric history			
Primiparity	21 (72.4)	24 (96.0)	45 (83.3)
History of stillbirth	0	1 (4.0)	1 (1.9)
Miscarriage	3 (11.3)	2 (8.0)	5 (9.3)
Drug use in pregnancy			
Maternal folic acid in pregnancy	29 (100)	23 (92.0)	52 (96.3)
Maternal iron in pregnancy	6 (20.7)	5 (20.0)	11 (20.4)
Maternal medication in pregnancy other than iron or folic acid	3 (10.2)	4 (16.0)	47 (87.0)
Maternal tobacco use	1 (3.4)	5 (20.0)	6 (11.1)
Maternal recreational drug use	0	1 (4.0)	1 (1.9)
Family history			
Family history of congenital abnormalities	1 (3.4)	2 (8.0)	3 (5.6)
Family history of hypertension	0	6 (24.0)	6 (11.1)
Family history of diabetes mellitus	0	6 (24.0)	6 (11.1)
Maternal medical history			
Maternal gestational diabetes in previous pregnancy	2 (6.9)	0	2 (3.7)
Maternal epilepsy	2 (6.9)	0	2 (3.7)
Maternal hypothyroidism	0	1 (4.0)	1 (1.9)

Table 4.20 Comparison of maternal factors between infants with HIE and non-HIE NE (continued)

	Infants with moderate-severe HIE according to expert criteria at two years (%) N=29	Infants with NE without HIE (%) N=25	All infants with NE (%) N=54
Maternal illness during index pregnancy			
Maternal infection during pregnancy	8 (27.6)	0	8 (14.8)
Maternal group B streptococcus colonisation	3 (10.3)	3 (12.0)	6 (11.1)
Maternal anaemia	6 (20.7)	4 (16.0)	10 (18.5)
Maternal antepartum haemorrhage	3 (10.3)	1 (4.0)	4 (7.4)
Maternal gestational diabetes mellitus	1 (3.4)	6 (24.0)	7 (13.0)
Maternal gestational proteinuria	2 (6.9)	3 (12.0)	5 (9.3)
Maternal pre-eclamptic toxaemia	2 (6.9)	2 (8.0)	4 (7.4)
Antenatal imaging			
Detailed antenatal USS done	29 (100)	25 (100)	54 (100)
Abnormal antenatal USS	3 (10.3)	3 (12.0)	6 (11.1)

4.7.2.2 Labour and delivery

Infants with HIE were more likely to have induction (20.7% versus 12.0%), augmentation with syntocinon (13.8% versus 12.0%) or assisted delivery (79.3% versus 56.0%) although they were less likely to have a malpresentation (3.4% compared to 8.0%).

Table 4.21: Comparison of labour and delivery between infants with HIE and non-HIE NE

	Infants with moderate- severe HIE according to expert criteria at two years (%) N=29	Infants with NE without HIE(%) N=25	All infants with NE (%) N=54
Augmentation and induction of labour			
Induction	6 (20.7)	3 (12.0)	9 (16.7)
Syntocinon	4 (13.8)	3 (12.0)	7 (13.0)
Presentation			
Cephalic presentation	28 (96.6)	23 (92.0)	51 (94.4)
Malpresentation	1 (3.4)	2 (8.0)	3 (5.6)
Method of delivery			
Spontaneous vaginal delivery	6 (20.7)	11 (44.0)	17 (31.5)
Instrumental delivery	5 (17.0)	10 (40.0)	15 (27.8)
Elective Caesarean	1 (3.5)	2 (8.0)	3 (5.6)
Emergency Caesarian in labour	7 (24.1)	3 (12.0)	10 (18.5)
Emergency Caesarian not in labour	1 (3.4)	0	1 (1.9)

In the infants with HIE there was a history of a sentinel event in 6 infants (20.7% of infants with HIE), with the most common of these being sudden profound bradycardia. Other sentinel events reported were placental abruption in four infants (13.8 %), uterine rupture in one infant (3.4 %). There were no sentinel events in the non-HIE NE group.

Table 4.22: Comparison of sentinel events between infants with HIE and non-HIE NE

	Infants with moderate-severe HIE according to expert criteria at two years (%) n=29	Infants with NE without HIE (%) N=25	All infants with NE (%) N=54
Sentinel event	6 (20.7)	0	6 (11.1)
Sudden profound bradycardia	5 (17.2)	0	5 (9.3)
Abruption	4 (13.8)	0	4 (7.4)
Uterine rupture	1 (3.4)	0	1 (3.4)
Maternal haemorrhage	2 (6.9)	0	2 (3.7)

4.7.2.4 Fetal distress

Meconium stained liquor (41.4% versus 32.0%), reduced fetal movements (41.4% versus 12.0%), and CTG abnormality (96.6% versus 64.0%) were more common in the infants with HIE, whilst maternal pyrexia and raised C-reactive protein were less common (3.4% versus 16.0%). Infants with HIE were much more likely to be small for gestational age (weight <9th centile (62.1% compared to 16.0%) and to have a relatively small head (<9th centile) (17.2 % compared to 4.0%).

Table 4.23: Comparison of miscellaneous markers of fetal distress with HIE and non-HIE NE

	Infants with moderate-severe HIE according to expert criteria at two years (%) . n=29	Infants with NE without HIE (%) N=25	All infants with NE (%) N=54
Maternal pyrexia in labour	1 (3.4)	4 (16.0)	5 (9.3)
Maternal blood culture positive	1 (3.4)	0	1 (1.9)
Maternal raised C reactive protein	1 (3.4)	4 (16.0)	5 (9.3)
Meconium stained liquor	12 (41.4)	8 (32.0)	20 (37.0)
Reduced fetal movements	12 (41.4)	3 (12.0)	15 (27.8)
CTG abnormality	28 (96.6)	16 (64.0)	44 (81.5)
pH in first hour <7.1	17 (58.6)	13 (52.0)	30 (55.6)
pH in first hour <7.0	9 (31.0)	10 (40.0)	19 (35.2)
Birthweight 2nd-9th centile	18 (62.1)	4 (16.0)	22 (40.7)
Birthweight 0.4-2nd centile	1 (3.4)	1 (4.0)	2(3.7)
Occipito-frontal circumference 2nd - 9th centile	5 (17.2)	1 (4.0)	6 (11.1)
Occipito-frontal circumference 2nd-0.4th centile	1 (3.4)	0	1 (1.9)

4.8 Validity analyses of epidemiological case definitions

The main purpose of the analyses was to determine the proportion of HIE cases who met the criteria for previous case definitions and to assess the impact of previous case definitions on ascertainment. Case ascertainment or identification within the context of the study involved identifying all cases of HIE firstly through the reviewers, and then secondly on basis of other existing research case-definitions. Completeness of case ascertainment is defined as the extent to which all the cases are determined and is an indication of how well current epidemiological case definitions perform when compared to the study reference standard. This provided a framework for comparing or interpreting previous work based on the clinical research definitions used in this study. The following abbreviations are used below: True positives (TP), false positives (FP), true negatives (TN), false negatives (FN). Specificity was calculated using the formula: Specificity = TN/TN+FP. Sensitivity was calculated using the formula: Sensitivity = TP/(TP+FN).

4.8.1 Validity analysis of TNS definition

Table 4.24 Validity analysis of TNS definition of HIE

	HIE according to expert criteria at two years	No HIE according to expert criteria at two years
TNS positive	23 (TP)	11(FP)
TNS negative	6 (FN)	14 (TN)

The specificity of the TNS definition of HIE was found to be 56.0%. The sensitivity of the TNS definition of HIE was found to be 79.3%.

4.8.2 Validity analysis of NNAP definition

Table 4.25: Validity analysis of NNAP definition of HIE

	HIE according to expert criteria at two years	No HIE according to expert criteria at two years
NNAP positive	28 (TP)	11 (FP)
NNAP negative	1 (FN)	14 (TN)

The specificity of the NNAP definition of HIE was also found to be 56.0%. However the sensitivity of the NNAP definition of HIE was found to be 96.6%.

Chapter 5: Discussion

5.1 Introduction

HIE was first described in 1976[42] and advances in treatment have led to reduction in death and disability[122]. However the estimated incidence of HIE according to reports from high-resource countries remains unchanged. HIE is a complex clinical syndrome that involves multiple physiological processes[24]. There are many gaps in our understanding of the aetiology of HIE, particularly the relative importance of intrapartum hypoxia and other factors, and this has led to difficulty in defining it clearly and consistently and in studying the aetiology without incurring bias due to assumptions.

Making an accurate diagnosis of HIE has always been a priority in epidemiological surveillance and has become an increasing clinical priority in the last decade with the advent of therapies such as therapeutic hypothermia. This has clear implications for identifying trends and identifying appropriate patients for treatment. Early diagnosis can be challenging especially in the context of the absence of a gold standard investigation and limitations in the sensitivity and specificity of the existing investigations. MRI is often used as a supporting investigation; however MRI is not currently sensitive enough to be used as a gold standard reference for HIE.

This study stemmed from local questions raised by the investigators and participants of The Neonatal Survey about the validity of existing epidemiological definitions of HIE and the wider challenges of epidemiological study of HIE. The literature review conducted at the start of this study confirmed that there are gaps in our understanding of the defining features and aetiology of HIE. The aim of this thesis was to address these gaps to explore the features of a cohort of infants with HIE, in order to define the natural history of the condition and to identify possible risk factors. Nonetheless, difficulties remain in studying a condition

which is not completely understood and these will be discussed in detail. Detailed study of HIE might also have an impact on improving accurate clinical detection of HIE, which could have important implications for both neonatal management and prediction of subsequent complications such as cerebral palsy[148].

5.2 Discussion of findings

5.2.1 Defining features of HIE

It was discussed in section 1.6.1 that existing studies have in the main identified infants with HIE by a single or group of clinical, biochemical, neurophysiological and/or radiological characteristics assumed to reflect perinatal hypoxia. The first challenge in this study was to identify a study cohort of infants representative of all infants with HIE without making assumptions and incurring the bias prevalent in many previous studies. In order to achieve this, neonatal discharge summary data from an unselected population was reviewed in a systematic way by the author. This study period (July 2010 - June 2011 inclusive) was specifically chosen to ensure that electronic neonatal discharge summary use was underway (commenced in 2006-2009 in most units) and therefore as reliable as possible. The neonatal deaths in all infants with NE numbered 6 (9.2%). This was very similar to the 9.1% observed in the Western Australian study[142]. All cases of HIE and non-HIE NE in this cohort were seen by clinicians working in the respective neonatal units. A number of measures were taken to minimise bias. All available notes were reviewed by the author (tertiary neonatal unit registrar with training and experience in assessment of neonatal neurology) and clinical data were collected using a standardised proforma developed by the author. Presenting symptoms were clearly categorised according to the inclusion criteria for suspected encephalopathy. Results of investigations were also classified where a classification system was available. The risk of missing non-HIE NE cases was minimised by including information arising after the neonatal period in the first two years of life.

5.2.1.1 Review of clinical diagnosis of HIE by expert panel

The panel discussed clinical features of HIE described in the existing literature and recognised evolution of the diagnostic criteria over time. The expert panel noted that there is potential for over-diagnosis of HIE, as the clinical characteristics of this cohort often fit the TOBY criteria for HIE superficially when they were better described by non HIE NE. Hence, unlike previous work this work identified potential sources of error in the clinical utility of the reference standard in routine clinical practice especially across different levels of seniority and experience of doctors and unit levels of expertise. In particular the following were noted as potential sources of error: neurological examination technique, aEEG interpretation, and access to aEEG for SCBUs.

5.2.1.2 Development of reference standard for HIE by expert panel and application of standard to cohort

The expert panel process identified a reference standard for clinical diagnosis of moderate-severe HIE, which allowed more systematic analysis of cases of HIE than has been possible in earlier studies. They were able to agree on markers of hypoxia as well as features of encephalopathy. They stated the need to incorporate all available information at a time point and within this study discussed data available at each of three time points (six hours of age, 72 hours of age and two years of age). Application of the reference standard to the cohort led to the identification of 54 infants out of 153 who had NE and of these 29 fulfilled the reference standard criteria for HIE. The criteria were applied retrospectively using the available data although there were often missing data items which might lead to misleading results.

It is important to consider factors that may allow a distinction between HIE and non-HIE NE cases. This was done more effectively in this study than many studies to date which have used a small selected (eg. radiologically) population rather than taking a population-based approach. An important question is whether the initial symptoms are different between cases and non-cases. The first symptoms may therefore be a relative discriminator for clinicians to suspect

and investigate cases appropriately. This is especially important when considering potentially reversible and treatable conditions, such as rare metabolic conditions. The commonest presentation of HIE was abnormal conscious level which was reported in 29 (100%) of infants with HIE as compared to 11 (44.0%) of infants with non-HIE NE. Conversely in non-HIE NE, abnormal limb movements was more likely to be the presenting symptom with 18 (72.0%) non-HIE infants compared to 9 (31.0%) of HIE infants. These abnormal limb movements were described as seizures. However this study did not explore the accuracy of diagnosis of seizures. This may be an important feature in differentiating between HIE and non-HIE NE. Infants with HIE were more likely to have an Apgar score of less than 6 at five minutes (22 (75.9%), need for any ventilatory resuscitation, need for ventilatory resuscitation at 5 minutes and need for ventilatory resuscitation at 10 minutes. In comparison with infants with moderate-severe HIE, infants with non-HIE NE more often developed epilepsy (16.0% compared to 3.4%), moderate-severe developmental delay (32.0% compared to 6.9%), and cerebral palsy (16.0% compared to 13.8%). Post mortem examination was performed in 4(13.8%) of infants with HIE. Previous estimates, mainly from the Southern hemisphere, range from 19% to 83%[113]; the lower rate found here may reflect the differing attitudes towards voluntary post mortem in different countries.

5.2.1.3 Validity of epidemiological definitions

In section 1.6.2 the theme of multiple epidemiological definitions of HIE was discussed. The validity of The Neonatal Survey definition of HIE was estimated to be 56.0% (specificity) and 79.3% (sensitivity) while the validity of the Neonatal Audit Project definition was found to be 56.0% (specificity) and 96.6% (sensitivity). While this suggests a very favourable result for the NNAP definition, it should be noted that the validity of the NNAP definition is very much reliant on the quality of Badgernet® data and this estimate based on a small sample may be an overestimate. During the course of this study it was found that the quality of Badgernet® data was very variable between units, seniority of doctor inputting data, and system experience of unit. This might lead to misleading results from

using this data for surveillance. In contrast, the TNS uses notes review to identify objective features; this is less prone to reporter bias.

5.2.2 Aetiology of HIE

This study is one of very few studies of the aetiology of HIE in an unselected population of infants. In section 1.6.3 the existing knowledge about the aetiology of HIE is discussed along with the limitations of studies using selected populations and/or making assumptions about aetiology. It provides some initial information on discriminating indicators between cases of HIE and cases of neonatal encephalopathy due to other causes, although the small sample size means an increased possibility of type II error[149]. Hence analysis of a larger series of cases from a systematic study or studies will be required to determine the significance of these findings.

5.2.2.1 Intrapartum hypoxia

Section 1.6.4 discussed possible markers of intrapartum hypoxia that have been studied previously in HIE and the results of larger studies that have looked at associations in populations of infants with NE or HIE. In this study, 11.1% of infants with NE had a sentinel event in comparison with only 7.9% in the Western Australian cohort[142,143]. None of the infants in the non- HIE NE subgroup had a sentinel event. Meconium stained liquor (41.4% versus 32.0%), reduced fetal movements (41.4% versus 12.0%), and CTG abnormality (96.6% versus 64.0%) were more common in the infants with HIE, whilst maternal pyrexia and raised C-reactive protein were less common (3.4% versus 16.0%).

5.2.2.2 Other factors

Demographically the infants with HIE were similar to the infants with non-HIE NE although they were less likely to live in an area with high index of multiple deprivation or to have an unemployed mother (48.3% compared to 64.0%) and were slightly more likely to be male (62.1% compared to 57.4%). Infants with HIE were much more likely to be small for gestational age (weight <9th centile (62.1%

compared to 16.0%) This was similar to the findings of the Western Australian study[142,143]. It was also found that infants with HIE were more likely to have a relatively small head (<9th centile) (17.2 % compared to 4.0%). This finding has been observed previously[142,143] and could reflect a fetal developmental abnormality predisposing to HIE or alternatively failure of protection of brain growth from an insult during fetal life. These findings do not indicate the nature of such an insult although it seems unlikely that chronic partial hypoxia were involved as no infants displayed evidence of this on MRI. There was an association between maternal pyrexia and NE in 9.3% of infants, similar to the 11.0% seen in the Western Australian study[142,143]. Interestingly, most of these were in the non-HIE NE group.

5.3 Study limitations

The author acknowledges that there are limitations within this thesis and these are described in detail throughout. However, several of these limitations warrant further discussion.

Firstly, this was a hospital NNU based study with case ascertainment relying on neonatal discharge summary documentation. The data quality of this documentation is monitored locally with no local or national standards. During the course of this study the data quality and completeness was found to be very variable. No robust alternative system is in place at national, regional or unit level to enable checking of the data quality. Patients who did not present to an NNU but instead elsewhere such as the emergency department could have been missed. It is known that most patients present with HIE before discharge from hospital but, given policies that advocate early discharge following birth, it is possible that infants might present after discharge to the emergency department leading to underestimation of incidence. Inclusion criteria were also based on previous studies which have indicated an age of onset of up to 96 hours and a minimum gestation in most cases of 35 weeks. It is possible that some late onset and /or preterm cases were missed. In addition analysis excluded cases whose notes were not available and this may influence the analysis, although there were only a small number of such cases. Discharge summaries were reviewed

manually by a single reviewer (the author) to minimise bias. However the discharge diagnosis stated on the discharge summary is likely to have led to observer bias. This may have led to under-ascertainment of cases not coded as HIE and over –ascertainment of cases coded as HIE.

The criteria for clinical identification of cases as discussed by the expert panel were simplified into criteria for use in the study and this may have led to the under-identification of cases by the use of an over-strict definition. There remains the potential that there may be markers of hypoxia which are as yet unknown and this may have led to misclassification of HIE cases as non-HIE NE.

The infants were assessed on the basis of clinical need and not in a standard way. Assessors included clinicians of all levels, who may have received variable levels of training in neonatal neurological assessment. There were often occasions where assessment was not documented or where the nature of the assessment was not clear. The quality of information recorded regarding the neurological examination was often limited in both quantity and quality. Investigative tests were only included if the test had been offered. The number of infants tested varied widely depending on the test. This may have led to observer bias as if NE was not suspected by clinicians, an infant may not have been offered a relevant test such as aEEG. The results of neuro- radiological, aEEG and EEG investigations were reviewed by the author wherever available; reports were reviewed where raw data was not available. This may have led to inconsistency in the results because there is evidence that the aEEG findings in HIE may not infrequently, be misclassified. Due to cost, reports of local placental histology and post-mortem reports were used without standardisation of interpretation of reports by central pathological review. There may be a potential for bias as a result of this, based on the presumption that those in non-specialised centres may not be as confident at reporting intricate or unusual changes. The MRI changes in HIE are also multiple and although these have been documented, the imaging has not been reviewed by a neuropathologist in all cases and the true distribution of changes has not been studied in detail in this study. MRI changes were classified by me into basal ganglia and thalamus distribution or cortical distribution. There was varying amounts of information available regarding the

clinical course, particularly if an infant was transferred to a unit outside the study. Information available about long term course varied widely. During the two year study period, some infants had clearly documented follow up throughout this time including a formal developmental assessment at two years if they met local criteria for this. However, most infants were not followed up to this extent and so the information about their course over this period is missing.

Furthermore, use of panels to achieve diagnostic consensus is known to have limitations[150]. There is a possibility of confirmation bias when using diagnostic consensus to study aetiology of a condition using a reference standard which incorporates markers which are thought to reflect hypoxia. This might have been improved by formal consensus methods, which would have the advantage of previous use and experience although there are potential disadvantages of time and expense, and lack of evidence of a clear benefit[151]. All of the panel members were clinical neonatologists, with no representation of other professionals with expertise in NE either clinical (eg neurologists) or academic (eg epidemiologists). Only four to five members were available for each panel, as opposed to the five to ten members recommended for good content validity[152,153] and time and expense precluded larger panel meetings. The content validity of the consensus in this study was limited as it is recommended that 80% of experts must agree on an item in order to achieve content validity when there are at least ten experts participating in consensus development[152,153].

In addition the lack of a control group makes it difficult to fully explore associations between exposures and HIE and to compare prevalence of exposure with data from previous studies.

5.4 Conclusions

5.4.1 Summary of findings

Evidence suggests that a clear consistent epidemiological definition of HIE is important in the surveillance of HIE[5] and the identification of trends in incidence. In addition, it has long been apparent that identification of aetiological factors in

HIE is important in order to understand the disease process and to identify potentially modifiable targets in antenatal and perinatal care. The work in this thesis explores the validity of existing epidemiological definitions and considers the role of potential aetiological factors. This has been achieved by means of a literature overview, a pilot study, case-note review, development of a reference standard by expert consensus, an observational study of possible aetiological factors, and an exploratory study investigating measurement of validity. The results show that it is feasible to construct a reference standard by expert consensus and to measure the validity of epidemiological definitions of HIE using this reference standard.

5.4.2 Implications for clinical practice

This study identified challenges in applying clinical diagnostic criteria in routine clinical practice especially by junior doctors and/or in SCBUs with less experience of HIE. These challenges relate to three aspects of care: neurological examination technique, aEEG interpretation, and access to aEEGs for SCBUs.

The quality of neonatal neurological examination might be improved by a number of possible measures. Training specific to the needs of infants with HIE might be offered as was done in the US study of total body hypothermia[44]. In the UK there are a number of neonatal neurology courses available to doctors including the British Paediatric Neurological Association NeoNATE course. Furthermore a systematic examination of tone and conscious level may be particularly relevant in NE. This might be facilitated by a neonatal neurological assessment tool. There are a number of neonatal assessment tools for the neurological assessment of newborn infants. Whilst each assessment tool has relative strengths and weaknesses, the Dubowitz[154] assessment is used in many centres as it has the advantages of being simple and quick, includes explanatory diagrams, can be used in sick infants, and gives an objective assessment of tone.

Many studies have found that aEEG interpretation is user dependent with an international survey of neonatologists showing that the majority of neonatologists are not confident in their ability to interpret the aEEG[155]. Studies have shown that

there is considerable disagreement between interpretation of individual grades of HIE on the EEG and aEEG of the same infants. Evans et al[156] showed that if aEEG alone was used to classify the severity of hypoxic ischaemic injury, 17% of those requiring treatment (4/23) would be missed, while 43% (10/23) of those with normal or mild traces, would be incorrectly labelled as having a moderate or severe encephalopathy.

This study identified the potential for over-diagnosis of HIE with potential repercussions. Out of the 25 infants with non-HIE NE, 2 (8.0%) received passive cooling and were transferred to a cooling centre with 1 (4.0%) going on to receive 72 hours therapeutic hypothermia (table 4.17). The number needed to treat for TH to prevent one death is six infants[121]. It is possible that over-diagnosis is contributing to this and the true number needed to treat is therefore lower. Therapeutic hypothermia is not without risk and has been reported to have unwanted side effects such as hypovolemia, glucose instability, pulmonary hypertension, and multisystem organ damage if applied to unaffected neonates. In addition it often necessitates transfer of the infant to a tertiary centre[122], with the attending risks associated with transporting a sick baby and disadvantages of mother-infant separation.

5.4.3 Implications for public health

HIE is a global problem causing significant morbidity and mortality. In low resource countries intrapartum hypoxia is likely to be the most significant aetiological factor and this is reflected in the much higher incidence of HIE in low resource countries and the effectiveness of measures to reduce intrapartum hypoxia.

This study adds further to the understanding that many cases of HIE may not be associated with intrapartum factors. It is difficult to use HIE as a reliable care quality marker without clear understanding of the relationship between care quality and HIE. This is an important consideration for clinicians who are being asked to take measures to reduce HIE as targets may not be appropriate without consideration of the wider aetiology of HIE.

5.4.4 Implications for further surveillance

An epidemiological approach to HIE is important to quantify the size of the problem and to monitor trends over time in order to obtain clues pertaining to potential geographical variation and risk exposure. Monitoring trends in the incidence of a potentially disabling and/or fatal condition is important to provide input to ensure guidelines are implemented for risk reduction. Additionally systematic study of this rare disease allows insight into the possible impact on the health care system in terms of potential health care needs and costs. The challenges involved in the diagnosis of HIE are multifactorial and in turn influence efficient surveillance of the disease. The importance of surveillance has increased in recent years with the increasing use of targets to drive quality improvement in clinical care. If the findings from this work are supported in future work, they may be applicable in epidemiological surveillance of HIE in the UK and other healthcare settings where there is routine perinatal data collection.

Current surveillance of HIE in the UK includes two approaches. Firstly the national TOBY disease register is for the purpose of TH and hence does not include infants who are deemed to be too unwell for TH. Secondly the NNAP is a national audit which relies on clinical identification of signs of NE and does not distinguish between NE and HIE. It needs to be supported by data source (Badgernet®) quality monitoring and its results should be interpreted in context and cannot be used to inform care quality improvement in order to prevent HIE. Thirdly the TNS was a regional survey which captured over twenty years of data using objective and universally documented criteria. Data collection for TNS has now ceased due to discontinuation of funding.

5.4.5 Implications for future research

There continues to be a need for a surveillance definition of neonatal encephalopathy which does not make assumptions about aetiology5 in order to not only improve surveillance but also to study aetiology. This study does not answer the question about causation and timing of hypoxia. However, it is clear

that infants who develop HIE must fail to protect their brains from hypoxia, at whatever point in fetal life it occurs.

In acute severe hypoxia such as occurs during a sentinel event, it seems likely that the healthy brain's defence mechanisms are overridden. In less acute or severe hypoxia, the timing and nature of the hypoxic insult may be less clear than its effects on the infant. As this has been extensively studied without identifying the nature of the hypoxic hit. It seems likely that there is a role for susceptibility of the individual fetus. This might be due to multiple genetic and/or environmental factors. There might be susceptibility at various points in the pathophysiological process: failure of cerebral autoregulation; primary energy failure excitotoxicity, secondary energy failure,

Impaired growth was found to be more common in infants with HIE than non-HIE NE in this study and in previous studies[142,143]. This might indicate poor growth due to another cause followed by vulnerability of the malnourished infant to withstand hypoxia to the brain. However the cause of poor growth has not been clear in these infants and the growth is not severely impaired; this degree of growth restriction might be the result rather than the cause of the hypoxic injury. This explanation is further supported by the finding in this study of corresponding "symmetrical" growth restriction of head growth which might relate to failure of the normal preservation of oxygen supply to the brain during systemic hypoxia.

Ideally the questions around definition and aetiology of HIE could be addressed in a prospective study. In view of the low incidence of the condition this would require a relatively long study period, financial sponsorship, and multicentre approach, in order to achieve sufficient sample size. A large population of infants with any features of NE could be identified prospectively. Case ascertainment could be improved by using multiple sources for surveillance[157] such as monthly questionnaires to professionals (eg ED clinicians, paediatricians, obstetricians, radiologists, neurologists), and/or existing surveillance units eg ToBy register, National Neonatal Audit Project. The completeness of ascertainment could be estimated by capture-recapture techniques[157].

A consistent and comprehensive approach to clinical assessment of the infant at each time point with detailed instructions highlighting the importance of complete neurological examination particularly with regard to tone, and systematic aEEG application and interpretation could be employed. This would provide more information with avoidance of the difficulties encountered in this study regarding missing information, variable quality of information, and under-ascertainment due to neonatal database quality. Causation could be studied which is not possible in a retrospective study. Data could be double entered to reduce errors in transcription. Expert panel consensus could be achieved by an established and systematic method such as the Delphi method with the advantage of a more objective and tested methodology. Such future studies may help to further define and study the aetiology of HIE.

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Appendix 1

NHS
Health Research Authority

NRES Committee East Midlands - Derby
Research Ethics Office
The Old Chapel
Royal Standard Place
Nottingham
NG1 6FS

Telephone: 01158839440
Facsimile: 01159123300

25 June 2012

Professor Elizabeth Draper
Professor of Paediatric and Perinatal Epidemiology
University of Leicester
Department of Health Sciences
22-28 Princess Rd West
Leicester
LE1 6TP

Dear Professor Draper

Study title:	**Hypoxic-ischaemic encephalopathy definition validation study.**
REC reference:	**12/EM/0218**
Protocol number:	**UNOLE 0320**

Thank you for your letter of 21 June 2012, responding to the Committee's request for further information on the above research.

The further information has been considered on behalf of the Committee by the Vice-Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non-NHS sites

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	Version	Date
Covering Letter		17 May 2012
Evidence of insurance or indemnity		17 May 2012
Investigator CV		
Other: CV for Elaine Boyle		
Other: CV for Pooja Harijan		
Other: CV for Jennifer Kurinczuk		
Other: Data Collection Form	9	14 May 2012
Other: System Level Security Policy	1	16 April 2012
Other: Information Security Policy Documentation	ISP-S1	
Other: Information Security Policy	4.1	09 October 2003
Protocol	8	03 May 2012
REC application		17 May 2012
Response to Request for Further Information		21 June 2012

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol

- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

Further information is available at National Research Ethics Service website > After Review

12/EM/0218	Please quote this number on all correspondence

With the Committee's best wishes for the success of this project

Yours sincerely,

Mr Peter Korczak (Chair)
Chair

Email: Sam.Tuite@nottspct.nhs.uk

Enclosures: "After ethical review – guidance for researchers"

Copy to: *Wendy Gamble*
Ms Carolyn Maloney, University Hospitals of Leicester NHS Trust
NIGB Ethics & Confidentiality Committee Secretariat

NIGB

Ethics and Confidentiality Committee

5th Floor, Skipton House
80 London Road
London
SE1 6LH
Tel: (020) 797 22557
Email: HRA.CAG@nhs.net

Professor Elizabeth Draper
Department of Health Sciences,
University of Leicester
22-28 Princess Road West,
Leicester
LE1 6TP

27 March 2013

Dear Professor Draper

ECC 5-05 (m)/2012 Hypoxic-ischaemic encephalopathy (HIE) definition validation study

Thank you for your application for approval under the Health Service (Control of Patient Information) Regulations 2002 to process patient identifiable information without consent. Approved applications enable the data controller to provide specified information to the applicant for the purposes of the relevant activity, without being in breach of the common law duty of confidentiality. The role of the NIGB Ethics and Confidentiality Committee (ECC) is to review applications submitted under these Regulations and to provide advice to the Secretary of State for Health (SofS) on whether an application should be approved, and if so, any relevant conditions. This application was considered on 19 September 2012.

Secretary of State decision

Following consideration of the ECC advice, reproduced below, the Secretary of State has determined that the application should be approved.

This letter should be read in conjunction with the outcome letter dated 03 October 2012.

Context

Application purpose

This research application from the University of Leicester detailed a study which aimed to improve the diagnostic precision of HIE in all settings by attempting to validate existing diagnostic criteria for HIE. Cases with features of neonatal encephalopathy would be manually identified using local electronic neonatal database discharge summaries. Around 300 patient profiles would be compiled, 45 of these would be anonymised and then submitted to a panel of local experts in order to generate a consensus diagnosis for each patient.

Confidential patient information requested

Support was requested in order to allow a researcher to access local electronic neonatal database discharge summaries of all infants born at 35 weeks or more gestation between 1 October 2008 and 30 September 2010. Patient details including name, hospital number, date of birth and date of death would be extracted.

ECC *conclusion*

Members considered the application at their meeting in September 2012 and agreed that consent would not be feasible for this activity and agreed to provide a recommendation of approval. This was subject to a satisfactory response to the following request for clarification:

Request for clarification

1. For each identifiable data item, please consider whether collection and retention is necessary and provide justification for each.

Further justification was provided by the applicant on the 16 October 2012 and forwarded to members who agreed that sufficient justification had been provided for all data items; however it was advised that postcode should be deleted once deprivation score had been calculated.

Conditions of support

1. Confirmation that consultation has taken place with a relevant patient group. **Confirmed.**

2. It should be ensured that demographic data can be and is separated from clinical data within the data collection sheet. **Accepted**

3. Confirmation of a favourable REC opinion. **Received**

4. Confirmation of satisfactory security arrangements. **Confirmed**

5. Postcode should be deleted once deprivation score has been calculated. **Accepted**

As the above conditions have now been accepted and met this letter provides confirmation of your final approval. I will arrange for the register of approved applications to be updated with this information.

Annual Review

Please note that this recommendation is subject to submission of an annual review report to show how you have met the conditions or report plans, and action towards meeting them. It is also your responsibility to submit this report on the anniversary of your final approval and to report any changes such as to the purpose or design of the proposed activity, or to security and confidentiality arrangements.

Important changes

Please note that the current administration of applications made under these Regulations by the NIGB Ethics and Confidentiality Committee is due to transfer to the Health Research Authority by 01 April 2013. Further information in relation to these arrangements can be found at http://www.hra.nhs.uk/hra-confidentiality-advisory-group.

Please do not hesitate to contact me if you have any queries following this letter, I would be grateful if you could quote the above reference number in all future correspondence.

Yours sincerely

Claire Edgeworth
NIGB Deputy Approvals Manager

Standard conditions

The approval provided by the Secretary of State for Health is subject to the following standard conditions.

The applicant will ensure that:

1. The specified patient identifiable information is only used for the purpose(s) set out *in the application.*

2. Confidentiality is preserved and that there is no disclosure of information in aggregate or patient level form that may inferentially identify a person, nor will any attempt be made to identify individuals, households or organisations in the data.

3. Requirements of the Statistics and Registration Services Act 2007 are adhered to regarding publication when relevant.

4. All staff with access to patient identifiable information have contractual obligations of confidentiality, enforceable through disciplinary procedures.

5. All staff with access to patient identifiable information have received appropriate ongoing training to ensure they are aware of their responsibilities.

6. Activities are consistent with the Data Protection Act 1998.

7. Audit of data processing by a designated agent of the Secretary of State is facilitated and supported.

8. The wishes of patients who have withheld or withdrawn their consent are respected.

9. The NIGB Office is notified of any significant changes (purpose, data flows, security *arrangements) to the application.*

10. An annual report is provided no later than 12 months from the date of your final confirmation letter. Details are available on the NIGB website.

11. Any breaches of security around this particular flow of data should be reported to the NIGB within 10 working days, along with remedial actions taken.

Appendix 3

NHS
Health Research Authority

Professor Elizabeth Draper
Department of Health Sciences,
University of Leicester
22-28 Princess Road West,
Leicester
LE1 6TP

msn@le.ac.uk

Skipton House
80 London Road
London
SE1 6LH

Tel: 020 797 22557
Email: HRA.CAG@nhs.net

20th March 2015.

Dear Professor Draper

Study title: **Hypoxic-ischaemic Encephalopathy (HIE) Definition Validation Study**
CAG reference: **ECC 5-05 (m)/2012**

Thank you for the provision of an annual review report for your research application, submitted for approval under Regulation 5 of the Health Service (Control of Patient Information) Regulations 2002 to process patient identifiable information without consent. Approved applications enable the data controller to provide specified information to the applicant for the purposes of the relevant activity, without being in breach of the common law duty of confidentiality, although other relevant legislative provisions will still be applicable.

The role of the Confidentiality Advisory Group (CAG) is to review applications submitted under these Regulations and to provide advice to the Health Research Authority on whether an application should be approved, and if so, any relevant conditions. The purpose of the annual review is to provide an update against the conditions of approval where applicable, confirm progress of the study, review the need to process confidential patient information, and ensure the minimum amount of identifiable information is being used.

Health Research Authority approval decision

The Health Research Authority, having considered the advice from the Confidentiality Advisory Group as set out below, has approved the continued processing of this application for the specified purposes until 31st December 2015, the expected end date for the study.

Context

This research application from the University of Leicester detailed a study which aimed to improve the diagnostic precision of HIE in all settings by attempting to validate existing diagnostic criteria for HIE. Cases with features of neonatal encephalopathy would be manually identified using local electronic neonatal database discharge summaries. Around 300 patient profiles would be compiled, 45 of these would be anonymised and then submitted to a panel of local experts in order to generate a consensus diagnosis for each patient. Support was requested in order to allow a researcher to access local electronic neonatal database discharge summaries of all infants born at 35 weeks or more gestation between 1 October 2008 and 30 September 2010. Patient details including name, hospital number, date of birth and date of death would be extracted.

Confidentiality Advice Team advice

Security arrangements

A satisfactory Information Governance Toolkit score of 76% was noted.

Steps taken to anonymise the information or obtain consent from individuals

It was noted the postcode would be deleted once the deprivation score was calculated for each case and demographic and clinical data was stored in separate databases.

There was still a continued need to access confidential patient information as specified within the original application.

Project Changes

It was noted there had been no changes to the data controller, purpose, scope, data flows, data sources or identifiable data items of the project.

Projected end date

It was noted the project was expected to end in December 2015 (i.e. the thesis submission date). It was noted that data collection would end before that date and data would be destroyed following publication of the study.

Confidentiality Advice Team advice conclusion

As a whole, it was recommended that the approval in place for the purposes set out in the application should continue for a further 12 months from the anniversary of the original final approval outcome letter, to the date specified above.

Annual Review

Please note that your approval is subject to submission of an annual review report to show how you have met the conditions or report plans, and action towards meeting them. It is also your responsibility to submit this report on the anniversary of your final approval and to report any changes such as to the purpose or design of the proposed activity, or to security and confidentiality arrangements. An annual review should be provided 4 weeks before the date indicated above.

Please do not hesitate to contact me if you have any queries following this letter. I would be grateful if you could quote the above reference number in all future correspondence.

Yours sincerely

Alison O'Kane
CAG Assistant
On behalf of the Health Research Authority

Email: HRA.CAG@nhs.net

Enclosures: Standard conditions of approval

NHS
Health Research Authority

Standard conditions of approval

The approval provided by the Health Research Authority is subject to the following standard conditions.

The applicant will ensure that:

1. The specified patient identifiable information is only used for the purpose(s) set out in the application.

2. Confidentiality is preserved and there are no disclosures of information in aggregate or patient level form that may inferentially identify a person, nor will any attempt be made to identify individuals, households or organisations in the data.

3. Requirements of the Statistics and Registration Services Act 2007 are adhered to regarding publication when relevant.

4. All staff with access to patient identifiable information have contractual obligations of confidentiality, enforceable through disciplinary procedures.

5. All staff with access to patient identifiable information have received appropriate ongoing training to ensure they are aware of their responsibilities.

6. Activities are consistent with the Data Protection Act 1998.

7. Audit of data processing by a designated agent is facilitated and supported.

8. The wishes of patients who have withheld or withdrawn their consent are respected.

9. The Confidentiality Advice Team is notified of any significant changes (purpose, data flows, data items, security arrangements) prior to the change occurring.

10. An annual report is provided no later than 12 months from the date of your final confirmation letter.

11. Any breaches of confidentiality / security around this particular flow of data should be reported to CAG within 10 working days, along with remedial actions taken / to be taken.

Appendix 4

The Leeds Teaching Hospitals NHS

NHS Trust

Amanda Burd

Research & Development

Leeds Teaching Hospitals NHS Trust
34 Hyde Terrace
Leeds
LS2 9LN

Tel: 0113 392 2878
Fax: 0113 392 6397

r&d@leedsth.nhs.uk
www.leedsth.nhs.uk

05/07/2013

Pooja Harijan
Room 106
Department of Health Sciences
22-28 Princess Road West
Leicester
LE1 6TP

Dear Pooja Harijan

Re: NHS Permission at LTHT for: Hypoxic-ischaemic encephalopathy definition validation study
LTHT R&D Number: PA13/10830
REC: 12/EM/0218

I confirm that *NHS Permission for research* has been granted for this project at The Leeds Teaching Hospitals NHS Trust (LTHT). NHS Permission is granted based on the information provided in the documents listed below. All amendments (including changes to the research team) must be submitted in accordance with guidance in IRAS. Any change to the status of the project must be notified to the R&D Department.

Permission is granted on the understanding that the study is conducted in accordance with the *Research Governance Framework for Health and Social Care*, ICH GCP (if applicable) and NHS Trust policies and procedures available at http://www.leedsth.nhs.uk/academic/research-development/

This permission is granted only on the understanding that you comply with the requirements of the *Framework* as listed in the attached sheet "Conditions of Approval".

If you have any queries about this approval please do not hesitate to contact the R&D Department on telephone 0113 392 2878.

Indemnity Arrangements

The Leeds Teaching Hospitals NHS Trust participates in the NHS risk pooling scheme administered by the NHS Litigation Authority 'Clinical Negligence Scheme for NHS Trusts' for: (i) medical professional and/or medical malpractice liability; and (ii) general liability. NHS Indemnity for negligent harm is extended to researchers with an employment contract (substantive or honorary) with the Trust. The Trust

only accepts liability for research activity that has been managerially approved by the R&D Department.

The Trust therefore accepts liability for the above research project and extends indemnity for negligent harm to cover you as investigator and the researchers listed on the Site Specific Information form. Should there be any changes to the research team please ensure that you inform the R&D Department and that s/he obtains an appropriate contract, or letter of access, with the Trust if required.

Yours sincerely

Dr D R Norfolk
Associate Director of R&D

Approved documents
The documents reviewed and approved are listed as follows

Document	*Version*	*Date of document*
NHS R&D Form	3.4	unsigned
SSI Form		N/A
Directorate Approval		N/A
Letter to NRES		21/06/2012
REC Letter confirming favourable opinion		25/06/2012
NIGB Letter		27/03/2013
Protocol	V7	30/04/2012
HIE Collection Form	V9	14/05/2012

Cc: Sharon English

Northampton General Hospital NHS
NHS Trust

05 July 2013

Research & Development Centre
Cliftonville
Northampton
NN1 5BD
Tel 01604 545941
Fax 01604 603143

R&D Manager: Mrs Julie Wilson

Dr Fiona Thompson
Consultant Paediatrician
Northampton General Hospital NHS Trust
Cliftonville
Northampton NN1 5BD

Dear Dr Thompson

Full title of study: **Hypoxic-ischaemic encephalopathy definition validation study**
REC Reference: **12/EM/00218**

Thank you for responding to the Sub-Committee's request for further information on the above research.

I have considered the further information on behalf of the Sub-Committee, and I am pleased to confirm that there are no outstanding issues and that you have NHS permission for this research at Northampton General Hospital NHS Trust.

Approved documents

NHS permission for the above research has been granted on the basis described in the application form, protocol and supporting documentation. The documents reviewed and approved were:-

- NRES Committee East Midlands – Derby – ethical approval letter dated 25/06/2012
- NHS R&D Form – Lock Code: 88196/361024/14/558
- NHS Site Specific Information Form – Lock Code: 88196/448258/6/773/173195/271579
- CVs – Fiona Thompson; Dr Pooja Harijan; Professor Elizabeth Draper
- Confidentiality & Data Protection Toolkit – signed by Dr Thompson on 15/05/2013
- CV – Fiona Thompson
- University of Leicester Clinical Trial/Professional Indemnity Insurance dated 17/05/2012
- E-mail from Fiona Thompson to Michelle Spinks dated 03/07/2013
- E-mail from Michelle Spinks to Fiona Thompson dated 01/07/2013
- E-mail from Michelle Spinks to Pooja Harijan dated 28/06/2013
- E-mail from Pooja Harijan to Michelle Spinks dated 28/06/2013
- HIE Definition Validation Feasibility Study Data Collection Form – Version 9 dated 14/05/2012
- National Information Governance Board Ethics & Confidentiality Committee approval letter dated 27/03/2013
- University of Leicester Information Security Policy
- System Level Security Policy – Version 1 dated 16/04/2012
- Protocol – Version 8 dated 03/05/2012

I would like to formally remind you that in undertaking the project at this site, the research team must adhere to the responsibilities laid out in the Research Governance Framework for Health and Social Care (ref. DoH 2005), and the Trust's internal policies and procedures. The key responsibilities are laid out in the attachment to this letter, so please take time to read it. The Trust is required to monitor the progress of research, to ensure that it is conducted, recorded and reported in accordance with the Research Governance Framework for Health and Social Care (2005), the protocol and other legal and regulatory requirements.

Permission is only granted for the activities for which a favourable opinion has been given by the REC. All amendments (including changes to the local research team) must be submitted to the R&D Office for approval. However, the research sponsor, Chief Investigator, or local Principal Investigator at a research site, may take appropriate urgent safety measures in order to protect research participants against any immediate hazard to their health or safety. The R&D Office should be notified that such measures have been taken. This notification should also include the reasons why the measures were taken and the plan for further action. The R&D Office should be notified within the same timeframe of notifying the REC and any other regulatory bodies.

This study will be reviewed for possible disclosure to other statutory bodies which may require this information. If you wish to enquire about this please contact the R&D office.

Finally, can I please request that you advise the R&D Office if you are named in any papers that are published as a consequence of this research.

Best wishes.

Julie Wilson

Julie Wilson
R&D Manager

c.c. *Professor Elizabeth Draper, University of Leicester msn@le.ac.uk*
Dr Pooja Harigan, University of Leicester drpharijan@doctors.net.uk
Wendy Gamble, University of Leicester wg4@le.ac.uk

George Eliot Hospital NHS
NHS Trust

West Midlands (South) Comprehensive Local Research Network
Fourth Floor, West Wing (ACF40002)
University Hospitals Coventry & Warwickshire NHS Trust
University Hospital
Clifford Bridge Road
Coventry
CV2 2DX

11th September 2013

Dr Richard de Boer
George Eliot Hospital
College Street
Nuneaton
Warwickshire
CV10 7DJ

Dear Dr de Boer

Project Title: Hypoxic-Ischaemic Encephalopathy definition validation study
R&D Ref: WMS020513
REC Ref: 12/EM/0218

I am pleased to inform you that the R&D review of the above project is complete, and NHS permission has been granted for the study at George Eliot Hospital NHS Trust. The details of your study have now been entered onto the Trust's database.

The permission has been granted on the basis described in the application form, protocol and supporting documentation. The documents reviewed were:

Document	Version	Date
REC Favourable Opinion Letter		25TH June 2012
NIGB Favourable Opinion Letter		27th March 2013
Protocol	8.0	3rd May 2012
Data Collection Form	9.0	14th May 2012

All research must be managed in accordance with the requirements of the Department of Health's Research Governance Framework (RGF), to ICH-GCP standards (if applicable) and to NHS Trust policies and procedures. Permission is only granted for the activities agreed by the relevant authorities.

All amendments (including changes to the local research team and status of the project) need to be submitted to the REC and the R&D office in accordance with the guidance in IRAS. Any urgent safety measures required to protect research participants against immediate harm can be implemented immediately. You should notify the R&D Office within the same time frame as any other regulatory bodies.

It is your responsibility to keep the R&D Office and Sponsor informed of all Serious Adverse Events. All SAEs must be reported within the timeframes detailed within ICH-GCP statutory instruments and EU directives.

In order to ensure that research is carried out to the highest governance standards, the Trust employs the services of an external monitoring organisation to provide assurance. Your study may be randomly selected for audit at any time, and you must co-operate with the auditors. Action may be taken to suspend Trust approval if the research is not run in accordance with RGF or ICH-GCP standards, or following recommendations from the auditors.

You will be sent an annual progress report which must be completed in order to ensure that the information we hold on our database remains up to date, in line with RGF requirements.

I wish you well with your project. Please do not hesitate to contact me should you need any guidance or assistance.

Yours sincerely,

VACupples

Victoria Cupples
Research Management & Governance Facilitator

Enc: PI Agreement

Cc: Dr Pooja Harijan, Chief Investigator
Julie Faulkes, University of Leicester

Appendix 6

Sheffield Teaching Hospitals NHS
NHS Foundation Trust

20 December 2013

Dr Alan Gibson
Neonatal Intensive Care Unit
Jessop Wing
Tree Root Walk
Sheffield

Dear Dr Gibson

Project Authorisation
NHS Permission for Research to Commence

STH ref:	STH17339
REC ref:	12/EM/0218
Study title:	Hypoxic-Ischaemic Encephalopathy Definition Validation Feasibility Study
Chief Investigator:	Professor E Draper, University of Leicester
Principal Investigator:	Dr Alan Gibson, STH
Sponsor:	University of Leicester
Funder:	University of Leicester

The Research Department has received the required documentation as listed below:

1.	**Sponsorship Agreement** **Clinical Trial Agreement** **Material Transfer Agreement** **Funding Award Letter**	NA NA NA Funding letter from University of Leicester, 26 November 2013
2.	**Monitoring Arrangements**	NA
3.	**STH registration document**	REC Application Form 17 May 2012
4.	**Evidence of favourable scientific review**	University of Leicester
5.	***Protocol – final version***	V8, 03 May 2012
6.	**Participant Information sheet**	NA
7.	**Consent form**	NA
8.	**Letter of indemnity arrangements**	University of Leicester 17 May 2012
9.	**ARSAC certificate / IRMER assessment**	NA
10.	**Ethical review- Letter of approval from NHS REC**	Derby REC, 25 June 2012
11.	**Site Specific Assessment**	STH SSI Form
12.	**Clinical Trial Authorisation from MHRA**	NA
13.	**Evidence of hosting approvals**	
	- **STH Principal Investigator**	Dr A Gibson, 19 December 2013
	- **Clinical Director**	Mr A Galimberti, 06 December 2013
	- **Research Finance**	Mrs L Fraser, 05 December 2013
	- **Data Protection Officer**	Mr P Wilson, 21 August 2013
14.	**Honorary Contract/Letter of Access**	05 August 2013
15.	**Associated documents**	
	- **NIGB approval**	27 March 2013
	- ***Data collection tool***	V9, 14 May 2012
	- **Sponsorship Letter – University of Leicester**	16 April 2013
	- **CV – E Draper**	Undated
	- **CV – P Harijan**	27 November 2012

This project has been reviewed by the Research Department. NHS permission for the above research to commence has been granted on the basis described in the application form, protocol and supporting documentation on the understanding that the study is conducted in accordance with the Research Governance Framework, GCP and Sheffield Teaching Hospitals policies and procedures (see attached appendix).

Yours sincerely

Professor S Heller
Director of R&D, Sheffield Teaching Hospitals NHS Foundation Trust
Telephone +44 (0) 114 2265934
Fax +44 (0) 114 2265937

CC, Clare Pye and Julie Cook, OGN

University Hospitals Coventry and Warwickshire NHS Trust

Research, Development and Innovation Department
Director of R,D&I: Professor Chris Imray - Tel: 02476 96 5222
Head of R,D&I: Ceri Jones - Tel: 024 7696 5623
R,D&I Operations Manager: Tammy Holmes – Tel: 024 7696 6196
R,D&I Business Manager: Natasha Wileman - Tel: 02476 966197
Research Associate - Governance: Isabella Petrie - Tel: 02476 966202
R,D&I Administration Specialist: Hannah Williamson- Tel 02476 964995
Research Portfolio Development Manager: Deborah Griggs - Tel: 02476 96 6195

10th February 2014

Dr Kate Blake
Consultant Neonatologist
Neonatal Unit, 1st floor, West Wing,
UHCW NHS Trust
University Hospital
Clifford Bridge Road
Coventry
CV2 2DX

Dear Kate

Study Title: Hypoxic-Ischaemic encephalopathy definition validation study

Thank you for submitting the above study for consideration by the Research & Development Office. I am pleased to inform you that your study has been approved.

Approved documents
The documents approved for use in this study are:

Document	Version	Date
NHS SSI form	3.5	N/a
NHS R&D form	3.4	N/a
NHS REC form	3.4	N/a
Protocol	1	03/05/12
HIE definition validation feasibility study data collection form	9	14/05/12

Conditions of Approval

- Should you wish to make any changes to the documents listed above, you must obtain R&D approval prior to use.

- An Annual Progress Report (APR) should be submitted to the main research ethics committee (REC) once a year throughout the trial or on request by R&D. The first report is due on 10th February 15. In addition, for CTIMP studies, a Development Safety Update Report (DSUR) should be submitted to the MHRA and the REC once a year. Guidance on the DSUR can be found in SOP 41 'Preparation and Submission of Annual Progress Reports and Development Safety Update Reports'.

- Notification of any serious breaches of GCP or the trial protocol must be reported to the R&D Department and a DATIX Clinical Adverse Event form completed within 24 hours of any suspected breach being identified and confirmed.

Sponsorship & Indemnity
Your research is covered by NHS indemnity as set out in HSG(96)48.

Your project may be subject to ad hoc audit by our department to ensure these standards are being met.

May I take this opportunity to remind you that, as a researcher, you must ensure that your research is conducted in a way that protects the dignity, rights, safety and well-being of participants. Trust R&D Approval assumes that you have read and understand the Research Governance Framework and accept that your responsibilities as a researcher are to comply with it, the Data Protection and Health & Safety Acts.

The Trust wishes you every success with your project.

Yours sincerely

Ceri Jones
Head of Research, Development and Innovation

CC Caroline Maloney, University of Leicester
Pooja Harigan, University of Leicester
Copy to file

University of Leicester
Affiliated Teaching Hospital

Kettering General Hospital NHS
NHS Foundation Trust

Rothwell Road, Kettering, Northants NN16 8UZ
Main Switchboard: 01536 492000
Direct Dial: 01536 492692
Web: www.kgh.nhs.uk

Research Committee

9 June 2014

Dr P Rao
Consultant Paediatrician
Kettering General Hospital NHS Foundation Trust
Rothwell Road
Kettering
NN16 8UZ

Dear Dr Rao

Project: **Hypoxic–ischaemic encephalopathy definition validation feasibility study**
KGH Rdb: **381**
NRES: **12/EM/0218**
Sponsor: **University of Leicester**

Thank you for attending the Trust Research Committee on 14 April 2014 with Dr Pooja Harijan, SpR University Hospitals Leicester and presenting an informative overview of the study; for which you have agreed to act as Local Collaborator.

Subsequently we have received and accept the final SSI form for this site.

I am pleased to confirm that with effect from the date of this letter, the above study now has Trust Research & Development permission to commence at Kettering General Hospital NHS Foundation Trust subject to the following terms:

- **Access to BADGER database for screening for suitable research cases must be undertaken on site at Kettering General Hospital NHS Foundation Trust.**
- **Data Collection forms must be coded and patient identifiable data removed. The list of codes and the patient's identifying details should be retained at this site by the Local Collaborator.**
- **A Letter of Access must be in place for Dr Pooja Harijan, Specialist Registrar, University Hospitals Leicester prior to commencement of the study; this will be facilitated by the Research Governance Office.**
- **Payment must be met by the University of Leicester for the cost of patient case note retrieval. Invoice will be raised by Finance Department at the commencement of the study.**

The following documents have been reviewed and accepted:

Document	Version	Date
IRAS NHS R&D Form	88196/361024/14/558	Sept 2012
Research Protocol	8.0	3 May 2012
Data Collection Proforma	9.0	14 May 2012
NIGB approval letter	ECC 5-05 (m)/2012	27 March 2013
NRES approval letter	12/EM/0218	25 June 2012

Please be aware that any changes to these documents after approval may constitute an amendment. The process of approval for amendments should be followed. Failure to do so may invalidate the approval of the study at this Trust.

The project will be registered on our Trust Research Database.

The research must be conducted in accordance with the principles of the Research Governance, including relevant legislation e.g. Health and Safety, Data Protection, Clinical Trials Regulations 2004 (where applicable) and Trust policies.
As the project progresses, the Research Committee should be notified of any significant developments or protocol amendments, serious adverse events and actions taken. Research projects may be subject to monitoring and audit under the auspices of the Research Committee and other authorities.

Please notify the Committee on completion of the study and keep the Committee informed of any changes implemented as a result of research findings.

If you have any questions please do not hesitate to contact me or Linda Lavelle, Research Co-ordinator x2171.

Yours sincerely

Dr Gwyn McCreanor
Associate Medical Director Clinical Services,
Clinical Lead for Research

Cc Dr P Harijan, Specialist Registrar, University Hospitals of Leicester NHS Trust
Pooja.harijan@uhl-tr.nhs.uk

Prof Elizabeth Draper, Chief Investigator, Dept of Health Sciences, University of Leicester.
msn@le.ac.uk

Craig Macpherson, Costing and Development Accountant, Finance Dept. Glebe House, Kettering General Hospital NHS Foundation Trust
Craig.macpherson@kgh.nhs.uk

Jonathan West, IT Clinical Safety Lead, Deputy Caldicott Guardian. ICT. Kettering General Hospital NHS Foundation Trust
Jonathan.West@kgh.nhs.uk

Sherwood Forest Hospitals NHS
NHS Foundation Trust

R&D Office

Telephone: 01623 622515
Extension: 3313
E Mail: research.anddevelopment@sfh-tr.nhs.uk

King's Mill Hospital
Mansfield Road
Sutton in Ashfield
Nottinghamshire
NG17 4JL

Tel: 01623 622515
Join today: www.sfh-tr.nhs.uk

Date: 19th August 2014

Dr Pooja Harijan
Speciality Registrar
University Hospital Leicester NHS Trust
Women's and Children's Division
Leicester Royal Infirmary
LE1 5WW

Dear Pooja

Letter of access for research study "HIE".

As an existing NHS employee you do not require an additional honorary research contract with this NHS organisation. We are satisfied that the research activities that you will undertake in this NHS organisation are commensurate with the activities you undertake for your employer. Your employer is fully responsible for ensuring such checks as are necessary have been carried out. Your employer has confirmed in writing to this NHS organisation that the necessary pre-engagement check are in place in accordance with the role you plan to carry out in this organisation. This letter confirms your right of access to conduct research through Sherwood Forest Hospitals NHS foundation Trust for the purpose and on the terms and conditions set out below. This right of access commences on **20th August 2014** and ends on **19th August 2015** unless terminated earlier in accordance with the clauses below.

You have a right of access to conduct such research as confirmed in writing in the letter of permission for research from this NHS organisation. Please note that you cannot start the research until the Principal Investigator for the research project has received a letter from us giving permission to conduct the project.

You are considered to be a legal visitor to Sherwood Forest Hospitals NHS Foundation Trust premises. You are not entitled to any form of payment or access to other benefits provided by this organisation to employees and this letter does not give rise to any other relationship between you and this NHS organisation, in particular that of an employee.

While undertaking research through Sherwood Forest Hospitals NHS Foundation Trust, you will remain accountable to your employer University Hospital Leicester NHS Trust but you are required to follow the reasonable instructions of your nominated manager **Samantha Jones & Lynsey Judd, Research Nurse Team Leaders,** in this NHS organisation or those given on her behalf in relation to the terms of this right of access.

Where any third party claim is made, whether or not legal proceedings are issued, arising out of or in connection with your right of access, you are required to co-operate fully with any investigation by this NHS organisation in connection with any such claim and to give all such assistance as may reasonably be required regarding the conduct of any legal proceedings.

You must act in accordance with Sherwood Forest Hospitals NHS Foundation Trust policies and procedures, which are available to you upon request, and the Research Governance Framework.

You are required to co-operate with Sherwood Forest Hospitals NHS Foundation Trust in discharging its duties under the Health and Safety at Work etc Act 1974 and other health and safety legislation and to take reasonable care for the health and safety of yourself and others while on Sherwood Forest Hospitals NHS Foundation Trust premises. Although you are not a contract holder, you must observe the same standards of care and propriety in dealing with patients, staff, visitors, equipment and premises as is expected of a contract holder and you must act appropriately, responsibly and professionally at all times.

You are required to ensure that all information regarding patients or staff remains secure and *strictly confidential* at all times. You must ensure that you understand and comply with the requirements of the NHS Confidentiality Code of Practice (http://www.dh.gov.uk/assetRoot/04/06/92/54/04069254.pdf) and the Data Protection Act 1998. Furthermore you should be aware that under the Act, unauthorised disclosure of information is an offence and such disclosures may lead to prosecution.

Sherwood Forest Hospitals NHS Foundation Trust will not indemnify you against any liability incurred as a result of any breach of confidentiality or breach of the Data Protection Act 1998. Any breach of the Data Protection Act 1998 may result in legal action against you and/or your substantive employer.

You should ensure that, where you are issued with an identity or security card, a bleep number, email or library account, keys or protective clothing, these are returned upon termination of this arrangement. Please also ensure that while on the premises you wear your ID badge at all times, or are able to prove your identity if challenged. Please note that this NHS organisation accepts no responsibility for damage to or loss of personal property.

We may terminate your right to attend at any time either by giving seven days' written notice to you or immediately without any notice if you are in breach of any of the terms or conditions described in this letter or if you commit any act that we reasonably consider to amount to serious misconduct or to be disruptive and/or prejudicial to the interests and/or business of this NHS organisation or if you are convicted of any criminal offence. Where applicable, your substantive employer will initiate your Independent Safeguarding Authority (ISA) registration in-line with the phasing strategy adopted within the NHS (as from 26th July 2010 at the earliest). Once you are ISA-registered, your employer will continue to monitor your ISA registration status via the on-line ISA service. Should you cease to be ISA-registered, this letter of access is immediately terminated. Your substantive employer will immediately withdraw you from undertaking this or any other regulated activity and you MUST stop undertaking any regulated activity.

Your substantive employer is responsible for your conduct during this research project and may in the circumstances described above instigate disciplinary action against you.

Patient Advice & Liaison
01623 672222
pals.kmh@sfh-tr.nhs.uk

If your circumstances change in relation to your health, criminal record, professional registration or ISA registration, or any other aspect that may impact on your suitability to conduct research, or your role in research changes, you must inform the NHS organisation that employs you through its normal procedures. You must also inform your nominated manager in this NHS organisation.

Yours sincerely

Mrs Sam Jones
Research Nurse Team Leader

Research & Development Department, Sherwood Forest Hospitals NHS Foundation Trust

cc: HR Department at Sherwood Forest Hospitals NHS Foundation Trust
HR department of the substantive employer (and provider of honorary clinical contract, where applicable)

Patient Advice & Liaison
01623 672222
pals.kmh@sfh-tr.nhs.uk

Appendix 10

University Hospitals of Leicester NHS
NHS Trust

DIRECTORATE OF RESEARCH & DEVELOPMENT

Director: **Professor D Rowbotham**
Assistant Director: **Dr David Hetmanski**
R&D Manager: **Carolyn Maloney**

Research & Development Office
Leicester General Hospital
Gwendolen Road
Leicester
LE5 4PW

Direct Dial: (0116) 258 8351
Fax No: (0116) 258 4226
10/04/2013

Dr Elaine Boyle
University Hospitals of Leicester
Neonatal Service
Leicester Royal Infirmary
Leicester
LE1 5WW

Dear Dr Elaine Boyle/ Dr Pooja Harijan

Ref: **UHL 11218**
Title: **Hypoxic-ischaemic encephalopathy definition validation study.**
Project Status: **Project Approved**
End Date: **03/09/2014**

I am pleased to confirm that with effect from the date of this letter, the above study has Trust Research & Development permission to commence at University Hospitals of Leicester NHS Trust. The research must be conducted in line with the Protocol and fulfil any contractual obligations agreed with the Sponsor. If you identify any issues during the course of your research that are likely to affect these obligations you must contact the R&D Office.

In order for the UHL Trust to comply with targets set by the Department of Health through the 'Plan for Growth', there is an expectation that the first patient will be recruited within 30 days of the date of this letter. If there is likely to be a problem achieving this target, please contact the office as soon as possible. You will be asked to provide the date of the first patient recruited in due course. In addition, the Title, REC Reference number, local target recruitment and actual recruitment for this study will be published on a quarterly basis on the UHL Trust external website.

All documents received by this office have been reviewed and form part of the approval. The documents received and approved are as follows:

Description	Version
Other: Data Collection Form	V9 Dated: 14.05.2012
Other: System Level Security Policy	V1 Dated: 16.04.2012
Other: Information Security Policy Documentation	ISP-S1
Protocol	V8 Dated: 03.05.2012

Please be aware that any changes to these documents after approval may constitute an amendment. The process of approval for amendments should be followed. Failure to do so may invalidate the approval of the study at this trust.

Undertaking research in the NHS comes with a range of regulatory responsibilities. Please ensure that you and your research team are familiar with, and understand the roles and responsibilities both collectively and individually.

Documents listing the roles and responsibilities for all individuals involved in research can be found on the R&D pages of the Public Website. It is important that you familiarise yourself with the Standard Operating Procedures, Policies and all other relevant documents which can be located by visiting www.leicestershospitals.nhs.uk/aboutus/education-and-research

The R&D Office is keen to support and facilitate research where ever possible. If you have any questions regarding this or other research you wish to undertake in the Trust, please contact this office. Our contact details are provided on the attached sheet.

We wish you every success with your research.

Yours sincerely

Carolyn Maloney

Carolyn Maloney
R&D Manager

Encs: .R&D Office Contact Information

Appendix 11

DHFT Research & Development Dept. Issued 20 OCT 2014

Derby Hospitals NHS
NHS Foundation Trust

Royal Derby Hospital
Uttoxeter Road
Derby
DE22 3NE

Tel: 01332 340131
Minicom: 01332 254944
www.derbyhospitals.nhs.uk

Research and Development Office

TRUST APPROVAL LETTER

Dr John McIntyre
Clinical Director & Consultant Neonatologist
Neonatal Unit
Royal Derby Hospital NHS Foundation Trust
Uttoxeter Road
Derby
DE22 3NE

Dear Dr John McIntyre

Re: Hypoxic-ischaemic encephalopathy definition validation study

R&D Reference: DHRD/2014/076

The agreed Recruitment Target for this Study is: 30

Further to the Research Ethics Committee approval for the above study, I am pleased to confirm Trust management approval for you to proceed in accordance with the agreed protocol, the Trust's financial procedures for research and development and the Research Governance Framework (which includes the Data Protection Act 1998 and the Health & Safety at Work Act 1974).

Please supply the following information at the appropriate time points to Dr Teresa Grieve, Assistant Director of R&D via (dhft.randdadmin@nhs.net):

- The date of your first patient recruited to the study
- A report every six months if the study duration is greater than six months
- Notification of any SUSARS, amendments, urgent safety measures or if the trial is abandoned.
- Notification of end of the study and an end of study report.
- Details of any publications arising from this research project.

Please note that approval for this study is dependent on full compliance with all of the above conditions.

The 70 day Target Date for Recruiting the First Patient is 18th December 2014

The Government's Plan for Growth (March 2011) announced the transformation of incentives at local level for efficiency in initiation and delivery of research. As a result the NIHR have introduced research performance benchmarks: ***studies must recruit to time and target, and first patient must be recruited onto the study within 70 days of submission of local application.*** Trusts will be fined, otherwise penalised and funding withheld if these metrics

are not met. Please ensure you work towards recruiting the first patient by the above date, and inform us if you envisage any problems as we will endeavour to help you meet this target.

I would like to take this opportunity to wish you every success with this study.

Yours sincerely

P.P. **Dr Fran Game FRCP**
Director of Research & Development

Short Study Title: Hypoxic-ischaemic encephalopathy definition validation study

R&D Ref: DHRD/2014/076

In accordance with your application and subsequent R&D approval dated 20th **October 2014** the following documentation was reviewed and may therefore be used on the above study with Trust approval.

List of reviewed Documents:

Document	*Version*	*Date*
NIGB Approval letter		27 March2013
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only)		17 May 2012
CV for Dr Pooja Harijan		
CV for Dr John McIntyre		
REC approval letter		25 June 2012
DCF	9	14 May 2012
Protocol	8	3 May 2012
IRAS R&D Form	88196/361024/14/558	
Response to REC for further information		21 June 2012

Pilot study proforma 04/01/2011 version 2

Study number ☐☐☐

Time taken to review Badgernet discharge summary (minutes)	

	Yes	No
Use of Badgernet code related to HIE / encephalopathy		
Use of neurological diagnostic code or term in text for condition other than HIE		

Symptoms in 1st 96 hours of life:-		
Hypotonia		
Hypertonia		
Decreased conscious level		
Hyperalert state		
Abnormal limb movements		
Seizures		
Abnormal eye movements		

Appendix 13

HIE definition validation feasibility study data collection form

BABY'S DETAILS *(or hospital label)*

Surname

First name

Address

Postcode

Hospital number

NHS number

Date of birth *(dd/mm/yyyy)* **Time of birth** *(hh:mm)*

/ / 20 :

Birth weight *(g)* **Gestation** *(weeks + days)*

+

Study reference no.

Sex

- ☐ Male
- ☐ Female
- ☐ Indeterminate
- ☐ Not known

Birth order of **Multiplicity**

Ethnic group

- ☐ European
- ☐ Asian
- ☐ African or West Indian
- ☐ Mixed race
- ☐ Other
- ☐ Not known

Intended place of delivery

Hospital of birth

MOTHER'S DETAILS

NHS number

Date of birth *(dd/mm/yyyy)* **Age** *(years)*

/ / 19

ADMISSION DETAILS

Hospital of this admission

Date of admission **Time of admission**

/ / 20 :

Admitted from *(name of hospital, labour ward, home)*

Reason for admission (tick all that apply)

- ☐ Respiration
- ☐ IUGR
- ☐ Feeding
- ☐ Abnormal tone
- ☐ Abnormal conscious level
- ☐ Seizures
- ☐ *Congenital abnormality (specify)*
- ☐ Other *(specify)*

Type of transfer in

- ☐ In utero
- ☐ Flying squad
- ☐ Not known
- ☐ Ambulance
- ☐ None

DISCHARGE DETAILS

Date of discharge or death **Time of discharge**

/ / 20 :

Discharged to *(name of hospital, home, death, etc)*

Type of care *(for transferred babies)*

- ☐ Continuing care *(includes return to home unit)*
- ☐ Specialist care
- ☐ Cardiac care

1

MOTHER'S DETAILS

Date of booking

/ / 20

Height at booking (cm)

Weight at booking (kg)

Body mass index at booking (kg/m²)

Blood group

ABO **Rhesus**

Marital status ***(specify/write "missing")***

Occupation ***(specify/write "missing")***

Smoking history at booking ***(cigarettes/day)***

Alcohol history at booking ***(units/week)***

Recreational drugs ***(specify type & quantity)***

Date of last menstrual period

/ / 20

Agreed expected delivery date (EDD)

/ / 20

EDD according to last menstrual period

/ / 20

EDD according to ultrasound scan

/ / 20

PREVIOUS PREGNANCIES

No. of live births and stillbirths not including this preg

No. of spontaneous abortions

No. of medical/surgical terminations of pregnancy

No. of preterm births *(20 to 36+5 weeks gestation)*

No. of pregnancies

Drugs during pregnancy ***(specify indication, gestation)***

Fertility treatment for this pregnancy

Family history of mother and father – ***(first and second degree relatives ; specify relative affected)***

Seizures

Congenital abnormalities ***(specify)***

Neurological disorders ***(specify)***

Inherited metabolic disorders ***(specify)***

Hypertension

Diabetes mellitus

MATERNAL MEDICAL HISTORY PRE-PREGNANCY
(Tick all that apply)

- ☐ Hypertension
- ☐ Diabetes mellitus
- ☐ Gestational diabetes
- ☐ Epilepsy
- ☐ Hyperthyroidism *(specify last T3, T4, TSH)*
- ☐ Hypothyroidism *(specify last T3, T4, TSH)*
- ☐ Other thyroid disease *(specify)*
- ☐ Treatment for thyroid disease *(specify)*
- ☐ Congenital abnormalities *(specify)*
- ☐ Multiple births
- ☐ Other neurological disorders *(specify)*

INDEX PREGNANCY-RELATED DISEASE

- ☐ Infection (specify details)
- ☐ Hyperemesis requiring admission (specify details)
- ☐ Physical trauma (specify details)
- ☐ Anaemia(Hb<10g/dL)(specify gestation, Hb, treatment)
- ☐ Other (specify details)

INDEX PREGNANCY-RELATED DISEASE ctd

Gestation of onset (completed wks)

- ☐ Antepartum haemorrhage
  No. of episodes ☐☐
  Specify details of 3 worst episodes:-
  - ☐ Mild ☐ Moderate ☐ Severe ☐☐
  - ☐ Mild ☐ Moderate ☐ Severe ☐☐
  - ☐ Mild ☐ Moderate ☐ Severe ☐☐
- ☐ Gestational diabetes mellitus ☐☐
- ☐ Gestational hypertension (systolic BP>=140 mmHg or diastolic BP>=90mmHg) ☐☐
- ☐ Gestational proteinuria ☐☐

IF GESTATIONAL HYPERTENSION THEN ANSWER THE FOLLOWING:-

Urine dip result (no. of plusses) ☐

Urine spot protein (mg/dL) ☐☐☐

Urine timed collection (mg/day) ☐☐☐

Headache Y ☐ N ☐

Blurred vision Y ☐ N ☐

Abdominal pain Y ☐ N ☐

Thrombocytopoaenia (platelet count <150x10^9/litre) Y ☐ N ☐

(specify platelet count if <150) ☐☐☐

Alanine aminotransferase (iU/L) ☐☐☐☐

(specify if documented)

Sudden worsening of blood pressure / proteinuria/ any of above during pregnancy Y ☐ N ☐

(specifygestation and details)

Resolution of above after delivery *(specify)*

ANTENATAL CONCERNS *(specify Investigation and treatment below)*

Antenatal ultrasound abnormality	☐ Yes	☐ No	☐ N/K
Further antenatal ultrasound after detailed scan at approx 20/40	☐ Yes	☐ No	☐ N/K
Reduced foetal movements	☐ Yes	☐ No	☐ N/K
Threatened preterm labour	☐ Yes	☐ No	☐ N/K
Other *(specify)*	☐ Yes	☐ No	☐ N/K

INTRAPARTUM COURSE

Presentation

☐ Cephalic
☐ Occipitoposterior
☐ Face
☐ Brow
☐ Breech
☐ Shoulder
☐ Not known
☐ Compound

Date and time of onset of labour

☐☐/☐☐/20☐☐ ☐☐:☐☐

Induction **Reason**

Y ☐ N ☐

Date and time of induction

☐☐/☐☐/20☐☐ ☐☐:☐☐

Method of induction

Date and time when membranes ruptured

☐☐/☐☐/20☐☐ ☐☐:☐☐

Date and time when cervix fully dilated

☐☐/☐☐/20☐☐ ☐☐:☐☐

Date and time when placenta delivered

☐☐/☐☐/20☐☐ ☐☐:☐☐

Interval from rupture of membranes to delivery

☐☐☐ **Hours** ☐☐ **Minutes**

Length of first stage (hours)

☐☐☐

Length of second stage (hours)

☐☐☐

Maternal pyrexia (>=37.5 degrees Centigrade)

☐ Yes ☐ No

☐☐.☐ **Maximum in labour**

Maternal C-reactive protein (mg/L) on day of delivery

☐☐☐

Shoulder dystocia

☐ Yes ☐ No

Attempted methods of delivery (tick all that apply)

☐ Normal
☐ Forceps
☐ Ventouse
☐ Assisted breech
☐ Elective CS
☐ Emergency CS, labouring
☐ Emergency CS, not labouring
☐ Not known

Drugs in labour ***(specify dose, route, date, time)***

Anaesthesia (*specify dose, route, date, time, if epidural top-up time*)

Meconium at delivery

Y ☐ N ☐

ACUTE PERIPARTUM/POSTPARTUM EVENTS:-

☐ *Uterine rupture*
☐ Cord prolapse
☐ Maternal collapse *(specify cause, treatment)*

☐ Eclampsia *(specify antepartum /intrapartum /postpartum; specify treatment)*

☐ Ante/intra partum maternal haemorrhage *(specify amount)*

☐ Sudden profound bradycardia *(specify duration)*

☐ Born before arrival in hospital *(specify conditions)*

☐ Other *(specify)*

INTRAPARTUM MONITORING

Cardiotocogram (CTG) carried out ☐ Yes ☐ No

Date and time of last CTG prior to delivery

Start time

☐☐/☐☐/20☐☐ ☐☐:☐☐

End time

☐☐/☐☐/20☐☐ ☐☐:☐☐

Foetal blood scalp sample (document worst recorded) ☐ Yes ☐ No

pH ☐☐.☐☐
pCO2 (kPa) ☐☐.☐
pO2 (kPa) ☐☐.☐
Base excess ☐☐.☐

INTRAPARTUM MONITORING- CONTINUED

Grade of person making last comment regarding CTG

Last comment regarding CTG in notes

Placenta weight (kg)

☐☐ ☐

Placenta condition

Membranes condition

Cord:-

Condition

Length

No. of vessels ☐

TWIN PREGNANCIES ONLY:-

☐ Monochorionic ☐ Dichorionic

☐ Monoamniotic ☐ Diamniotic

☐ Twin-twin transfusion donor
☐ Twin-twin transfusion recipient

☐ Death of co-twin in utero *(give details below)*
☐ Death of co-twin ex utero *(give details below)*
☐ Other complication(s) of twin pregnancy *(specify)*

MATERNAL NOTES MAIN BODY (INCL LETTERS)

Consultant comments regarding CTG in labour

Y ☐ N ☐ *If yes specify*

Placenta histology sent *(specify result)*

Y ☐ N ☐

Placenta microbiology swab sent *(specify result)*

Y ☐ N ☐

NEONATAL CONDITION

Head circumference (cm) ☐☐.☐

Blood group

ABO ☐ Rhesus ☐

Apgar score at 1 minute ☐☐

Apgar score at 5 minutes ☐☐

Apgar score at 10 minutes ☐☐

Apgar score at 15 minutes ☐☐

Apgar score at 20 minutes ☐☐

Time to first gasp

☐☐ **minutes**

Time to regular respirations

☐☐☐ **minutes**

Resuscitation *(specify interventions and times)*

1st umbilical arterial gas **Age in Hrs** ☐☐☐

pH	☐.☐☐
pCO2 (kPa)	☐☐.☐
pO2 (kPa)	☐☐.☐
Base excess	☐☐.☐

1st umbilical venous gas **Age in Hrs** ☐☐☐

pH	☐.☐☐
pCO2 (kPa)	☐☐.☐
pO2 (kPa)	☐☐.☐
Base excess	☐☐.☐

1st capillary gas **Age in Hrs** ☐☐☐

pH	☐.☐☐
pCO2 (kPa)	☐☐.☐
pO2 (kPa)	☐☐.☐
Base excess	☐☐.☐

Date and time of admission

☐☐/☐☐/20☐☐ ☐☐ ☐☐

Reason for admission

Surfactant?

☐ Yes
☐ No
☐ Not known

NEONATAL PERIOD

Congenital anomaly (tick all that apply)

- ☐ None
- ☐ Chromosomal
- ☐ Genito-urinary
- ☐ Neural tube defect
- ☐ *Other neurological lesions*
- ☐ GIT upper (above diaphragm)
- ☐ GIT lower (below diaphragm)
- ☐ Craniofacial
- ☐ Cardiac
- ☐ Complex or multiple
- ☐ Other *(specify)*

NEONATAL PERIOD

Renal

Serum Creatinine on 1st day (micromol/L) ☐☐☐

Max serum creatinine

☐☐☐ **on** ☐☐/☐☐/20☐☐

Oliguria ☐ Yes ☐ No

Anuria ☐ Yes ☐ No

Other renal problems *(specify)*

Respiratory problems

Ventilation including O2 therapy ☐ Yes ☐ No

Invasive ☐

Non invasive ☐

O2 therapy ☐

Duration of ventilation ☐☐☐ hours

Maximum settings

Chest X-ray findings

Other respiratory problems *(specify)*

Haematology

Platelets on 1st day of life (x10⁹/L) ☐☐☐

Minimum platelet count (x10⁹/L)

☐☐☐ **on** ☐☐/☐☐/20☐☐

Mucosal bleeding ☐ Yes ☐ No

International Normalised Ratio (INR) on 1st day ☐☐

Maximum INR

☐☐ **on** ☐☐/☐☐/20☐☐

Other haematological problems *(specify)*

Cardiovascular problems

Hypotension ☐ Yes ☐ No

Inotropes *(specify dose and duration)* ☐ Yes ☐ No

Clinical cardiac failure ☐ Yes ☐ No

Other cardiovascular problems (*specify*)

Liver

Serum alanine aminotransferase (ALT) (iU/dL) on 1st day ☐☐☐

Max serum ALT

☐☐☐ **on** ☐☐/☐☐/20☐☐

Other liver problems *(specify)*

NEONATAL PERIOD

Drugs given eg. Morphine, dopamine, phenobarbitone

Drug	Maximum dose *specify units)*	Route

PARALYSIS

Age of starting paralysis* ☐☐☐ **hrs**

Age of stopping paralysis* ☐☐☐ **hrs**

***Record time of effective muscle relaxation**

COOLING

☐ Yes ☐ No

Age of decision to passive cool ☐☐☐ **hrs**

Age of starting passive cooling ☐☐☐ **hrs**

Duration of passive cooling ☐☐☐ **hrs**

Minimum temperature ☐☐.☐ **^{0}C**

Age of decision to actively cool ☐☐☐ **hrs**

Age of starting active cooling ☐☐☐ **hrs**

Duration of active cooling ☐☐☐ **hrs**

Minimum temperature ☐☐.☐ **^{0}C**

NEONATAL PERIOD

Suspected/proven Infections (specify)

FEEDING

Date/time gut priming started (<24ml/kg/day)

☐☐/☐☐/20☐☐ ☐☐ ☐☐

Date/time nasogastric feeding started (>=24ml/kg/day)

☐☐/☐☐/20☐☐ ☐☐ ☐☐

Date/time oral feeding started

☐☐/☐☐/20☐☐ ☐☐ ☐☐

Date/time oral feeding only

☐☐/☐☐/20☐☐ ☐☐ ☐☐

Feeding method at discharge (*tick all that apply*)

☐ Breast
☐ Bottle
☐ Nasogastric tube
☐ Other (*specify*)

Other morbidity (specify)

NEONATAL PERIOD

Cerebral function monitoring

Age started ☐ **days** ☐☐ **hrs**

Age stopped ☐ **days** ☐☐ **hrs**

Findings *(specify)*

Clinical seizures

Age of onset ☐☐☐ **hrs**

Type *(specify type of movement, other signs, Duration of individual seizures, frequency)*

Date/time of last seizure prior to discharge

☐☐/☐☐/20☐☐ ☐☐ ☐☐

Anticonvulsants on discharge *(specify)*

Electroencephalogram (EEG) report

Cranial Ultrasound Scan

☐ Yes ☐ No

Date

☐☐/☐☐/20☐☐

☐ Neonatologist ☐ Radiologist

Report

Magnetic resonance imaging (MRI)

No. of MRI scans during admission ☐

Date of MRI

☐☐/☐☐/20☐☐

☐ T1weighted ☐ T2 weighted

☐ Diffusion weighted ☐ MR spectra

Report

Sedation for MRI

If MR Spectroscopy carried out:-

No. of voxels

Areas of brain

Echo time

☐ Short

Other comments regarding technique

Report

PAEDIATRIC NOTES

Further brain imaging

☐ Y ☐ N

Date

☐☐/☐☐/20☐☐

Type(s)

Report (s)

Further Diagnoses

☐ Neurologist ☐ Neonatologist

☐ Other (specify)

Palliation

☐ Y ☐ N

Specify details

IF died state:-

Date and time

☐☐/☐☐/20☐☐ ☐☐ ☐☐

Causes stated on death certificate

natal notes *(tick box and describe)*	1st 6 hours	1st day 7-24h	2nd Day	3rd Day
Tone				
Normal				
Hyper				
Hypo				
Flaccid				
Other				
Unknown				
Consc level				
Normal				
Hyperalert, stare				
Lethargic				
Comatose				
Other				
Unknown				
Fits				
Number per day				
Treatment				
Posture				
Normal				
Fisting/cycling				
Strong distal flexion				
Decerebrate				
Other				
Unknown				
Moro				
Normal				
Partial				
Absent				
Other				
Unknown				
Grasp				
Normal				
Poor				
Absent				
Other				
Unknown				
Suck				
Normal				
Poor				
Absent/bites				
Other				
Unknown				
Respiration				
Normal				
Hyperventilation				
Brief apnoea				
Apnoeic				
Other				
Unknown				
Fontanelle				
Normal				
Full AND not tense				
Tense				
Other				
Unknown				
Date				
Time				
Time of last feed				

Study ref. no.

natal notes *(tick box and describe)*	4th Day	5th Day	6th Day	7th Day
Head				
O-F Circumference				
OFC centile				
Eyes				
Fontanelle				
"Fix"				
"Track"				
Squint				
Passive tone				
Sunset				
Nystagmus				
R/L Scarf sign				
R/L heel-ear angle				
R/L popliteal angle				
R/L ankles angle				
Adductor angle				
Neck repeated flexion				
Active tone				
Neck flexors				
Neck extensors				
Neck extensor/ hypertonia				
Axial tone				
Head control				
Arm grasp reaction				
Arm traction response				
Legs supporting/standing				
Legs "scissoring"				
Sitting pull-up				
Sitting alone <30secs				
Sitting alone >30secs				
"Falls back"				
Reflexes				
Root				
Suck				
Walk				
Moro				
Biceps				
Knee				
Clonus				
Propping				
Parachute				
Misc				
Fisting/cortical thumb				
Asymmetry arms				
Asymmetry legs				
Other				
Date				
Time				
Age (Hours)				
Time of last feed				

Study ref. no.

onatal notes *(tick box and describe)*

	8th Day	9th Day	10th Day	11th Day
Head				
O-F Circumference				
OFC centile				
Eyes				
Fontanelle				
"Fix"				
"Track"				
Squint				
Passive tone				
Sunset				
Nystagmus				
R/L Scarf sign				
R/L heel-ear angle				
R/L popliteal angle				
R/L ankles angle				
Adductor angle				
Neck repeated flexion				
Neck flexors				
Neck extensors				
Neck extensor/ hypertonia				
Active tone				
Axial tone				
Head control				
Arm grasp reaction				
Arm traction response				
Legs supporting/standing				
Legs "scissoring"				
Sitting pull-up				
Sitting alone <30secs				
Sitting alone >30secs				
"Falls back"				
Reflexes				
Root				
Suck				
Walk				
Moro				
Biceps				
Knee				
Clonus				
Propping				
Parachute				
Misc				
Fisting/cortical thumb				
Asymmetry arms				
Asymmetry legs				
Other				
Date				
Time				
Age (Hours)				
Time of last feed				

Study ref. no.

onatal notes *(tick box and describe)*

		12th Day	13th Day	14th Day	Day of Discharge
Head	O-F Circumference				
	OFC centile				
Eyes	Fontanelle				
	"Fix"				
	"Track"				
	Squint				
Passive tone	Sunset				
	Nystagmus				
	R/L Scarf sign				
	R/L heel-ear angle				
	R/L popliteal angle				
	R/L ankles angle				
	Adductor angle				
	Neck repeated flexion				
	Neck flexors				
	Neck extensors				
Active tone	Neck extensor/ hypertonia				
	Axial tone				
	Head control				
	Arm grasp reaction				
	Arm traction response				
	Legs supporting/standing				
	Legs "scissoring"				
	Sitting pull-up				
	Sitting alone <30secs				
	Sitting alone >30secs				
	"Falls back"				
Reflexes	Root				
	Suck				
	Walk				
	Moro				
	Biceps				
	Knee				
	Clonus				
	Propping				
	Parachute				
	Fisting/cortical thumb				
Misc	Asymmetry arms				
	Asymmetry legs				
Other					
	Date				
	Time				
	Age (Hours)				
	Time of last feed				

Free text (note section heading to which applies)

Appendix 14

Panel case proforma

For each case discussed please indicate your diagnosis at each of the three time points, indicating your rationale.

Age	HIE	Non-HIE NE
6 hours		
72 hours		
2 years		

Appendix 15

Table of definitions of data items

Data item	Definition
Preterm birth	Birth at less than 37 weeks gestation
Miscarriage	Spontaneous termination of pregnancy at less than or equal to 23 weeks
Drug use in pregnancy	Recreational drugs excluding alcohol/tobacco
Maternal medical history	Illnesses not including those secondary to pregnancy
Maternal medication in pregnancy	Any maternal medication taken at any time for any duration during pregnancy
Family history	Family in history in first degree relative
Ethnicity	Ethnicity of mother
Maternal infection during pregnancy	Any bacterial/viral/fungal infection
Detailed antenatal USS performed	Routine twenty week anomaly scan
Abnormal antenatal USS	Any abnormality on USS
Extra antenatal USS	USS other than dating and anomaly USS for any reason
Malpresentation	Any presentation other than cephalic
Need for ventilatory resuscitation	Non-invasive or invasive ventilation of any duration
Raw aEEG available	Raw aEEG (electronic or hard copy) available
Early MRI	MRI on day 1 to 4
Late MRI	MRI on day 5 onwards
Moderate/severe encephalopathy on aEEG	Patterns 2-5 in the TOBY aEEG classification system[84]
Electrical seizures on D1-D4 aEEG	abrupt, transient, sharp rise in the lower margin of aEEG (regardless of raw EEG)
EEG evidence of encephalopathy	Continuous EEG slowing consistent with encephalopathy
MRI basal ganglia changes	Any basal ganglia changes on T1W,T2W, or DWI imaging
MRI cortical ischaemic changes	Any cortical changes onf T1 W, T2W, DWI imaging
Passive therapeutic hypothermia	Cessation of temperature control devices eg incubator
Active therapeutic hypothermia	Cooling mattress use
Transfer for therapeutic hypothermia	Transfer to cooling centre
Epilepsy	Epilepsy according to treating clinician
Cerebral palsy	Static motor disability associated with insult to developing brain according to treating clinician

Moderate/severe developmental delay	Delay of at least six months in at least one domain of development
Death in neonatal period	Death before or up to the age of 28 days
Death before the age of 2	
Coroners post mortem performed	
Post mortem consistent with HIE	Post mortem consistent with HIE according to pathologist’s report