STUDY PROTOCOL

Scientific Title: **Relationship between brain structure and function of very preterm infants to predict neurodevelopmental outcome**

Short Title/Acronym: **PPREMO - Prediction of PREterm Motor Outcomes**

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Abbreviations:

AIMS	Alberta Infant Motor Scale;
BTSID III	Bayley Scales of Infant and Toddler Development
CA	Corrected age
CP	Cerebral palsy
Dubowitz	The Neurological Assessment of the Preterm and Full-term Newborn Infant
EEG	Electro-encephalogram
GA	Gestational age
GMs	General Movements Assessment
MND	Minor neurological deficit
MRI	Magnetic resonance imaging
NNNS	Neonatal Intensive Care Network Neurobehavioural Scale
NSMDA	Neuro Sensory Motor Development Assessment
PMA	post menstrual age
TIMP	Test of Infant Motor Performance

Rationale:

A major limitation in delivering timely interventions to improve outcomes for the infant born preterm, is early detection of problems and accurate prediction of motor outcomes. Infants born very preterm (≤30 weeks gestational age; GA) may experience significant motor difficulties with 10-15% developing cerebral palsy (CP) (Doyle 2004), a further 40- 50% having minor motor and behavioural difficulties (Holsti 2002, Williams 2010) and 30-60% experiencing cognitive difficulties at school age (Mathur 2009). Currently, a diagnosis of CP often only occurs well into the second year of life, reducing the ability to provide early intervention strategies at a time when they may be of most benefit to the developing brain.

Magnetic Resonance Imaging (MRI) at term equivalent age combined with General Movements assessment (GMs) at 12 weeks post term is currently the most accurate method of early and accurate prediction of cerebral palsy at 12 months corrected age (Spittle et al. 2009). To date there have been no studies comparing the use of earlier MRI combined with neuromotor and neurobehavioural

assessments (at 30 weeks GA) to predict later motor diffficulties including cerebral palsy (at 12-24 months corrected age; CA).

The most predictive neuromotor assessments in the neonatal period for detecting later CP are longitudinal GMs (writhing period from 28 weeks to 46 weeks PMA) combined with GMs in the fidgety period (12 weeks post term) (Darsaklis 2011, Noble and Boyd 2011, Burger 2009). The assessment with the best evaluative validity for assessing motor behaviour is the longitudinal assessment with the Test of Infant Motor performance (TIMP; 34 weeks GA to 16 weeks post term) (Noble and Boyd, 2011; Campbell 1995). The most valid neurobehavioural measures in the neonatal period are the Neontal Intensive care Network Neurobehavioural Scale (NNNS; Lester 2004) and the Assessment of Preterm Infants' Behaviour (APIB; Als 2005), however these have poor reliability and limited clinical utility (Noble and Boyd 2011). A combination of predictive motor and behavioural assessments may be required to enable earlier prediction of later CP and minor neurological dysfunction (MND; Spittle et al. 2008).

Magnetic resonance imaging (MRI) at term has been shown to be more accurate than serial ultrasound in predicting cerebral palsy (Woodward 2006, Mirmiran 2004) and is increasingly being used to identify brain injury following preterm birth. A combination of MRI, GMs and neurobehavioural assessments has demonstrated improved predictive validity over each of the tools individually and assists in understanding the relationship between brain structure and function (Constantino 2007). The recent introduction of MRI compatible incubators allows earlier safe scanning of preterm infants, and together with the addition of diffusion imaging techniques, means it is now possible to obtain structural connectivity information in the preterm period. The relationship of this early brain structure with later neuromotor, neurodevelopmental, and cerebral palsy outcomes is not yet clear. However, new developments in the non-invasive, cotside test of EEG, namely the use of dense array EEG that allows calculation of source localisation, provides new insights, when fused with the structural and functional MRI data, into brain development and the relationship between structure and function.

Motor assessements with the best specificity and sensitivity to detect CP, and to correctly identify those without CP (or distinguish typical /delayed motor development), at 8-12 months, are the Alberta Infant Motor Scale (AIMs) (Piper 1994) and the Neurosensory Motor Development Assessment (NSMDA, Burns 1989). The best assessment for discriminating between typical and atypical cognitive, language and motor (gross and fine) development at 24 months CA is the Bayley III (Bayley N 2006;). The combination of the AIMs, NSMDA and Bayley III can be used to discriminate outcome as CP or minor motor delay, compared to typical motor development at 12 months CA (Spittle 2008, Greene 2012).

To date no study has determined the most accurate tools at 30 weeks GA to predict later CP and differentiate children with minor motor difficulties from typically developing children. In our proposed study we will utilise a combination of predictive neuromotor and neurobehavioural assesments, and advanced brain imaging techniques (MRI) to predict later abnormal motor development (CP, minor motor difficulties). Earlier confirmation of a diagnosis of CP or minor motor difficulties may lead to tailoring of early interventions to enable better outcomes by school age.

Aims:

Brain **structure** refers to the quantitative (diffusion imaging, HARDI model) and qualitative (classification of white and grey matter injury using traditional clinical sequences) MRI findings, and EEG data. Brain **function** relates to the neurological (Dubowitz neurological assessment), neuromotor (General Movement's assessment, The Test of Infant Motor Performance), neurobehavioural (NICU Neonatal Neurobehavioural Assessment) and visual assessment findings. Neurodevelopmental outcomes measure cognition, language skills and motor development (The Bayley Scales of Infant and Toddler Development III, the Alberta Infant Motor Scale, the Neurosensory Motor Developmental Assessment). Our aims involve the relationships between brain structure and function at each of the different timepoints, and then their predictive abilities of later outcomes.

Primary Aims:

In our cohort of infants born at less than 30 weeks, and a term reference group, we aim to examine:

1. The relationship between brain structure and function at 30 and 40 weeks.

2. The predictive relationship between early functional measures at 30 and 40 weeks and brain structure on the 30 week MRI; with neuromotor outcome at 12 weeks corrected age.

3. The predictive relationship between the combination of brain structure and function at 30 weeks, 40 weeks, and 12 weeks corrected age; with neurodevelopmental outcome at 12 months corrected age.

Secondary Aims:

- The relationship between General Movement assessments trajectories and diffusion imaging at term age.
- Development of motor and/or sensory (or visual) connectivity between 30wk and 40wk MRIs in infants with and without brain lesions.
- Examine the relationship between visual skills at 40 weeks C.A. and brain structure

Study Design:

A prospective longitudinal cohort study of 120 preterm infants born <30 weeks GA and a reference group of 20 healthy, term born infants.

Study Sample:

Infants will be recruited from the Royal Brisbane and Women's Hospital, Grantley Stable Neonatal Intensive Care Unit, which is one of four neonatal intensive care units in Queensland, Australia. Infants born at ≤30 week's gestation will be eligible for this study if they have no major congenital or chromosomal abnormalities that could adversely affect their neurodevelopmental outcome. Follow up assessments after discharge will be completed in families' homes or at the hospital and therefore they will be required to live within a 200km radius of the hospital. Families need to be English speaking as we do not have funding for translators.

A group of 20 healthy, term born infants will be recruited as a reference group, from the Royal Brisbane and Women's Hospital or interested volunteers via word of mouth.

Sample Size calculations

We have based our sample size calculations on the landmark paper of Spittle et al 2009, where they investigated the ability of MRI at term equivalent age, and the General Movement's assessment, to predict motor outcomes and cerebral palsy at 12 months corrected age. This is the most appropriate data available for sample size calculations as no data are available to assess the relationship between MRI at 30 week and motor outcome and CP at 12 months corrected age.

Their cohort of infants born at less than 30 weeks gestational age had a sample size of n=86. MRI was classified into normal, or mild, moderate or severe white matter abnormality (WMA). Infants with normal or mild WMA were grouped, and infants with moderate and severe WMA were grouped. All infants with moderate or severe WMA developed cerebral palsy by 12 months corrected age. We also know from the literature that 10% of infants born at less than 30 weeks gestation will develop cerebral palsy (Doyle 2004)

We are planning a study of independent cases and controls with 7.6 controls (MRI normal or with mild/moderate WMA) per case (MRI with moderate/severe WMA). Prior data indicate that the failure rate among controls is 0.05. If the true failure rate for experimental subjects is 0.5, we will need to study 8 experimental subjects and 60.8 control subjects to be able to reject the null hypothesis that the failure rates for experimental and control subjects are equal with probability (power) 0.9. The Type I error probability associated with this test of this null hypothesis is 0.05. We will use an uncorrected chi-squared statistic to evaluate this null hypothesis.

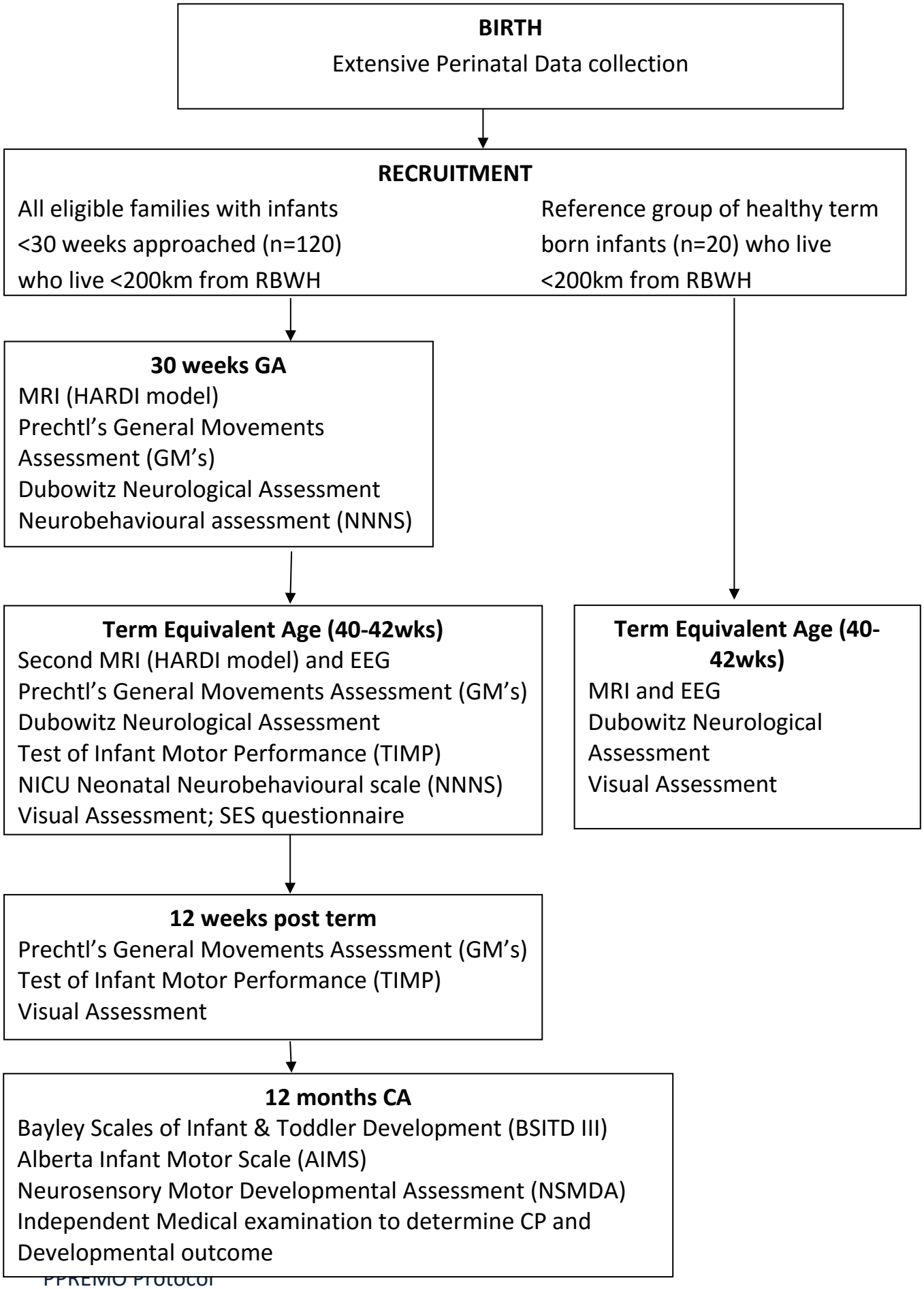
As we then wish to explore WMA at 30 weeks gestational age and its ability to predict CP at 12 months we will require an increase in the projected numbers, and a further 20-30% to account for attrition.

Recruitment Procedure:

Infants will be enrolled within a week of birth, after medically stable and parental consent is obtained. Parents and/or caregivers will be introduced to the study by a medical staff member on the ward, who will also provide them with an information leaflet explaining the study. If they are interested in hearing more about the study, a member of the research team will approach them with a full information pack, explain the study in detail and answer any questions they may have. Informed consent will be obtained from those families who wish to participate in the study, and their child will be formally enrolled.

Healthy term born infants will be recruited shortly after birth, to serve as a typically developing comparison group. They will be assessed with the same measures at term

Consort Flow Chart of Timelines:



Perinatal data collection:

For all infants enrolled in the clinical study an extensive record of the pregnancy, birth history, and neonatal course, including respiratory, cardiovascular and nutritional history will be collected. E.g. Gestational age at birth, birthweight, small for gestational age (birth weight<10th percentile), gender, multiple birth status, cranial ultrasound findings, proven or suspected necrotising enterocolitis, maternal antenatal corticosteroid administration, postnatal corticosteroid use, use of oxygen at time of discharge from hospital, and postmenstrual age at NICU discharge. These data will be collected from their medical discharge summary in their medical records and will be later compared to outcome (predictors). Socio-demographic information such as maternal and paternal education and occupation, will be collected using a baseline parent questionnaire.

Clinical Measures:

Measures can be categorised into discriminative, predictive and evaluative tools (Kirshner 1985, Spittle 2008). In order to answer research questions appropriately, it is essential to select tools whose properties are designed for the purposes you are using them for. A discriminative tool distinguishes between infants developing typically and those who are not; a predictive tool enables prediction of future performance, based on current performance; and an evaluative tool allows evaluation of changes over time and is often used to evaluate change as a result of treatment exposure. The primary purpose of this study is to identify what combination of measures, and new techniques, are available to improve early prediction of later outcomes; and discrimination between those infants which are developing typically and those who are not (i.e. CP and MND.

Magnetic Resonance Imaging (MRI):

Brain MRI will be performed using a 3.0−T Siemens Trio and the MRI−compatible incubator currently in use at the Royal Brisbane and Women's Hospital. The infants will be fed, fitted with earmuffs to minimize noise exposure, then carefully wrapped and placed in the incubator in the scanner without sedation or anaesthesia. The scanning duration will be about 45-50 minutes for each baby. A series of advanced brain imaging sequences will be acquired (T1, T2, HARDI) and will allow us to explore several aspects of brain microstructure and function: i) Regional and global cortical surface and thickness; ii) White matter organisation (Diffusion weighted imaging) ; iii) Functional and structural connectivity of relevant areas (e.g. sensori−motor cortex, visual cortex, thalamus) ; iv) Brain representation of visual and somatosensory function (block design paradigm and resting state functional MRI). MRI data will be analysed with image processing techniques.

Electroencephalography (EEG)

EEG will be collected using equipment used in clinical EEG acquisition. The EEG system, NicOne (Nicolet, USA) collects, amplifies, displays and stores the digital data. The electrodes used to capture the data on the scalp will be either (i) silver-silver chloride electrodes held in place with EEG paste as used in standard clinical recordings or (ii) commercially available EEG caps, where the electrodes are built in to a baby bonnet that is the correct size to fit the head. The electrodes are pre-moistened to facilitate electrode-skin contact and there is no abrasion to the skin. This system is in current use by us in other research protocols in the RBWH nursery. The EEG, once collected, will be subjected to advanced research analysis, specifically to allow spatial localisation of the sources of the EEG which will be examined together with the MRI data to enhance interpretation of brain function. Establishing a recording involves some handling of the baby over a several minute period and then leaving the baby at rest for about a 30-60 minute period of recording.

Dubowitz Neurological Assessment

The Dubowitz Neurological assessment was developed for the assessment of term and preterm infants at risk of developmental delay (Dubowitz 1980). It is a discriminative assessment with a continuous score from 0-34, where scores <30 are classified as abnormal (ref). Neurological assessments are not as predictive of later neurodevelopmental outcome, but play an important role in rapid diagnosis of neurological disorders in the newborn period, and guide medical management (Cioni et al 1997c). The infants in this study will have the Dubowitz neurological assessment at 30 weeks gestation, and term equivalent age.

General Movements Assessment (GMs)

The General Movements Assessment is a predictive and discriminative tool that involves observation of the infant's spontaneous motor activity (Einspieler 2004). It can be used from preterm birth until 20 weeks corrected age and is carried out by videoing the infant in a calm alert state, with no external stimulation. Scoring is completed from the recording with a total of approximately 5 minutes of movement needed to be seen in order to score (3 full movement sequences are required for pattern recognition). In the early preterm stage this may require up to an hour of video in order to select sequences of active movement, but at term and 12 weeks corrected it may only take a few minutes. The infants in this study will have 1-2 assessments of their GMs in the preterm period (30 and 32 weeks PMA), 1 assessment at term equivalent age, and 1 at 10-12 weeks corrected age.

Movements are classified as normal or abnormal (poor repertoire, cramped synchronised or chaotic) in the writhing period from preterm up to 6 weeks post term. During the fidgety period from 9-20 weeks post term, fidgety movements are classified as present, abnormal or absent. General Movements have been shown to have high specificity (96%) and sensitivity (95%) in predicting cerebral palsy (Prechtl et al, 1997b; Darsaklis 2011; Burger 2009) and are also being used to predict minor neurological dysfunction (Hadders-Algra 2004).

A relationship between abnormal General Movements in very preterm infants, and cerebral white matter abnormalities on structural MRI has been found by Spittle (2009) and their ability to predict CP at 12 months post term (Constantino 2007). To date no studies have looked at the relationship between diffusion imaging of brain connectivity, and the spontaneous movements of premature infants and their ability to predict CP.

The NICU Network Neurobehavioural Scale (NNNS)

The NICU Network Neurobehavioural Scale is designed to provide information relating to an infant's development, behavioural maturation, central nervous system integrity and stress responses (Lester and Tronic 2004). Although based on Brazelton's Neonatal Behavioural Assessment Scale (Brazelton 1995), the NNNS also draws on many other assessments, including: Prechtl's Neurological Examination of the Full-Term Infant; Amiel Tison's Neurological Examination of the Maturity of Newborn Infants; Korner and Thom's Neurobehavioural Assessment of the Preterm Infant, and Als, Tronic and Brazelton's Assessment of Preterm Infant Behaviour (Als 2005).
The NNNS was specifically designed for a Maternal Lifestyle Study however, the authors intended the scale to be used with both low and high-risk infants, including preterm infants (Lester 2002). Administration and scoring of the NNNS requires certification. Test-retest reliability has been established with preterm infants.

Neonatal Visual Assessment (Guzetta)

The neonatal assessment of visual functions provides useful information on various aspects of early neonatal visual function, including ocular motility, fixation, following, acuity and attention at distance. The battery is easy to perform, does not require long training, and can be performed reliably from 32 weeks post menstrual age (Ricci 2010). It has been demonstrated to contribute to prediction of neurodevelopmental outcome in preterm babies (Ricci 2008, 2011; Mercuri 1999).

Test of Infant Motor Performance (TIMP)

The TIMP is a discriminative and evaluative test of functional motor behaviour used to assess infants between the ages of 34 weeks postconceptional age and 4 months post-term (Campbell 1995, 2001). The test assesses the postural and selective control of movement needed for functional motor performance in early infancy and is norm referenced. Observational and elicited items are administered in a standardised procedure and the test takes 20-40 minutes to administer. In this study, the TIMP will be performed at term equivalent age, and at 12 weeks corrected age. At 12 weeks corrected age, the TIMP has been shown to predict 12-month motor performance with sensitivity 92% and specificity 76% (Campbell 2002) and preschool motor performance (mean age 4.75 years) with sensitivity 72% and specificity 91% (Kolobe 2004).

Neurodevelopmental and motor outcome at 12 months:

These assessments will be performed at the child's home, when they reach 12 months corrected age. No single measure has been shown to provide conclusive data on attainment and quality of motor skills to a reference population of preterm born infants from term to 24 months corrected age, and therefore a combination of the following 3 assessments will be used.

Medical Assessment:

Infants in this study will be independently assessed by a paediatrician experienced in infant development. The purpose of this assessment is to discriminate which infants are developing typically from those who are not, and to confirm diagnoses of CP or not CP. In cases of CP, motor type and distribution will be recorded, and severity established through classification with the Gross Motor Function Classification System (GMFCS) (Badawi 1998). Any additional medical diagnoses that have been made by this stage will be recorded.

Bayley Scales of Infant and Toddler Development III (Bayley III)

The Bayley III is a discriminative tool designed to assess cognitive, language and motor development (Bayley 2006). It can be used to give an overall developmental outcome, or can be divided into motor index, cognitive index and language index subsets. It is a norm referenced test used to describe the current developmental functioning of the infant. Normative data taken from large samples of typically developing children are used for comparison and to indicate areas and severity of any delays (Bayley 2006). The Bayley III involves interaction between the child and the examiner in a standardised series of play tasks, and takes 45-60 minutes to administer at 12 months CA.

Neurosensory Motor Developmental Assessment (NSMDA)

The NSMDA is a discriminative and predictive, criterion-referenced test of gross and fine motor development (Burns 1989, Spittle 2008). It examines gross and fine motor performance, neurological status, posture, balance and response to sensory input. The examiner observes and administers items and the test takes 10-30 minutes to complete. The results give a total score and a functional classification of motor development as normal, or with mild, moderate or severe problems of posture, movement and co-ordination. It has good sensitivity (80%) and specificity (56%) at 4 months compared with medical diagnosis at 24 months (Burns 1989)*. Studies looking at the longer term predictive validity of the NSMDA, found assessment at 8 months to have an 80% sensitivity of outcomes at 11-13 years in extremely low birth weight infants with no apparent neurological deficit/CP (Danks 2012).

Alberta Infant Motor Scale (AIMS)

The AIMS is a discriminative, norm referenced tool that tests gross motor skills through the components of weight bearing, posture and antigravity movements (Piper 1994, Campbell 1995, 2002). The test takes 10-30 minutes to administer and involves observation of the infant in prone, supine, sitting and standing. The AIMS is an appropriate assessment tool for monitoring the gross motor development of typically-developing infants and has normative data based on a population of 2200 infants from 0-18 months in Alberta, Canada (Piper 1994). Normative data for preterm infants

has also been published with a sample of 800 infants born at ≤32 weeks from the Netherlands (van Haastert 2006). The AIMS has excellent inter-rater, intra-rater and test-retest reliability for full term and preterm infants (Blanchard 2004, Jeng 2000). The AIMS has excellent reliability, content, construct and concurrent validity with the BSID-II (r = 0.98) (Jeng 2000, Bartlett 2003, Piper 1992, 1994). Although the AIMS was not designed as a predictive tool, it has moderate to excellent predictive validity, depending on the age of assessment (Darrah 1998, Jeng 2000). The AIMS will be used to classify each infant's development as normal or suspicious/abnormal at 12 months corrected age.

Outcome/ Study benefits:

Earlier identification of infants at high risk of cerebral palsy will ensure appropriate services are engaged to support the infant and family at an earlier stage, therefore reducing the family burden. These infants may be able to be referred on to appropriate diagnostic services at an earlier stage, receive an accurate diagnosis at an earlier stage, and enable targeted early interventions to be employed. This will optimise the critical period of brain development, ensure the best outcomes are achieved from early intervention programs, and ensure families are adequately supported in this difficult stage. It will also allow further research to develop intervention programs to meet the needs of these infants and their families.

Reliability of assessment tools

(Spittle 2008, Noble 2011)

Assessment Tool	Test-retest	Interrater	Intrarater	Internal consistency
GMs	100% global judgement, 85% for analysis of 20 general movement recordings after time interval of 2y	89–93% agreement for 11 studies (total n=358), average kappa=0.88 for term–20 weeks (total n=92), kappa=0.85–0.94 for preterm infants (n=39)	kappa=1.00 3–26 weeks (n=20),36 kappa=0.90 (preterm GMs), kappa=0.96, (writhing GMs), kappa=0.92 (fidgety GMs)	n/a
Dubowitz	n/a	>96% agreement reported	n/a	n/a
NNNS	r=0.33–0.44 for infants 34, 40, 44 weeks PMA	n/a	n/a	n/a
TIMP	r=0.89 34 weeks PMA–4mo (n=106)	ICC=0.95 age not specified (n=21)	ICC=0.98–0.99 age not specified (n=21)	On Rasch analysis for version 5: 34 weeks' PMA–4mo (n=990) person separation index 5.20, reliability 0.96
BSITD III	2-4mo (n=50) FM *r*=0.67, GM *r*=0.77 9-13mo (n=50) FM *r*=0.86, GM *r*=0.86	n/s	n/s	1-12mo norm.pop. (n=1700) FM *r*0.77-0.89, GM *r*=0.86-94 1-12mo atypical (n=688) FM *r*=0.90-0.92, GM *r*=0.93-0.96
AIMS	0-18mo (n=210) ICC=0.99	0-18mo (n=195) ICC=0.99 3-18mo (n=45) ICC=0.98-0.99	0-18mo (n=253) ICC=0.997 3-18mo (n=41) ICC=0.97-0.99 0-12mo (n=14) ICC=0.98-99	0-18mo (n=unclear) *R*=0.99

NSMDA	n/s	n/s	1–24mo (n=NR) r=0.80	n/s

AIMS, Alberta Infant Motor Scale; BTSID III, Bayley Scales of Infant and Toddler Development; Dubowitz, The Neurological Assessment of the Preterm and Full-term Newborn Infant; FM, fine motor; GM, gross motor; GMs, General Movements Assessment; ICC, intraclass correlation coefficient; NNNS, Neonatal Intensive Care Network Neurobehavioural Scale; NSMDA, Neuro Sensory Motor Development Assessment; n/a, not available; n/s, no study identified; PMA, postmenstrual age; TIMP, Test of Infant Motor Performance;

Evidence of content, construct, and concurrent validity (Spittle 2008, Noble 2011)			
Assessment Tool	**Content**	**Construct**	**Concurrent**
GMs	Experts in field	Theory supported by ultrasound studies Discriminates between infants with cerebral lesions and controls (n=22) Discriminates between normal and abnormal movements in term and preterm infants (n=130)	Term infants with HIE (*n*=58), 0-4mo: neurological exam %agree=78-83 Preterm infants (n=66), 0-4mo: neurological exam %agree=80 Preterm infants at 12 weeks corrected age (n=108) low-strength correlation with TIMP scores – Tau C=0.31.8 Preterm infants (n=86) WMA on MRI correlates with GMs at 1mo r=0.28, p<0.008; 3 mo r=0.48, p<0.001
Dubowitz	Review of previously existing assessments, literature review, experts in field	Discriminates between infants with neuromuscular disorders and CNS dysfunction. Clinical signs correlate with lesions identified with brain imaging. Repeated exams show age-related change	Preterm infants at term WMA via MRI associated with poor scores on Dubowitz (*n*=168; *p*=9.002). Preterm infants at term (*n*=66), overall cerebral abnormality on MRI correlates with poorer total Dubowitz scores *p*<0.01 Preterm infants perinatal risk rating (*n*=100), *r*=0.6132 (*p*<0.001), US *r*=0.5642 (*p*<0.001)

NNNS	Evolved from previous infant assessments including NBAS. Developed for a longitudinal study of prenatal drug exposure and child outcome in preterm and term infants	Discriminates between those infants exposed to drugs (cocaine, tobacco) and alcohol and those who are not (i.e. sensitive to neurotoxic effects)	Preterm infants at term (n=168) – increasing WMA via MRI associated with presence of non-optimal reflexes p<0.014
	Literature Review		
TIMP	Expert panel	Rasch analysis	Term and preterm infants (n=90)
	Literature review	Sensitive to age related change	3mo: AIMS r=0.64
	Elicited items occurred during caregiver interactions	Infants with medical risk factors score lower than peers	preterm infants 12 weeks corrected age (n=108) AIMS r=0.57, GMs tau C=0.31, term infants (n=108) ENNAS r=0.67
	Pilot studies and revision of content	Discriminates between infants with low and high risk of motor problems	
BSITD III	Literature review	Factor analysis	Typically developing infants (*n*=102)
	Expert panel	Scores increase with age	1–42mo: BSID-II *r*=0.60
	Pilot, national try-out, and standardization studies	Children with cerebral palsy and high risk of motor problems have lower mean scores than controls	Typically developing infants (*n*=81)
			2–42mo: PDMS-2 Total Motor *r*=0.55

AIMS	Literature review Expert panel Mailout to 291 members of Canadian Physiotherapy Association Pilot Study to test feasibility	Multidimensional scaling, item response theory and Guttman scaling Scores increase with age Rasch analysis demonstrated items ordered by increasing difficulty Preterm infants have lower scores than term infants Discriminates between normal, suspect, and abnormal development (*n*=60)	Typically developing infants (*n*=103) 0–13mo: BSID-II *r*=0.97 0–13mo: PDMS *r*=0.99 At-risk infants (*n*=68) 0–13mo: BSID-II *r*=0.93 0–13mo: PDMS *r*=0.95* Preterm infants (*n*=41) 6mo: BSID-II *r*=0.78 12mo: BSID-II *r*=0.90*
NSMDA	Literature review Developed by experts in the field	Factor analysis Consistency of results over time Discriminates between normal and abnormal development (n=148) Preterm infants with IUGR score lower than normal birthweight preterm infants (n=198)	Low-birthweight infants (n=148) 24mo: Ni significant difference between NSMDA and paediatrician's classification $\chi 2=0.08$

AIMS, Alberta Infant Motor Scale; BTSID III, Bayley Scales of Infant and Toddler Development; CNS, central nervous system; Dubowitz, The Neurological Assessment of the Preterm and Full-term Newborn Infant; EEG, electroencephalogram; ENNAS, Einstein Neonatal Neurobehavioural Assessment Scale; GMs, General Movements Assessment; HIE, hypoxic ischaemic encephalopathy; IUGR, intrauterine growth retardation; MRI, magnetic resonance imaging; NBAS, Brazelton Neonatal Behavioural Assessment Scale; NNNS, Neonatal Intensive Care Network Neurobehavioural Scale; NSMDA, Neuro Sensory Motor Development Assessment; PDMS, Peabody Developmental Motor Scale; PMA, postmenstrual age; r, Pearson's correlation coefficient; TIMP, Test of Infant Motor Performance; WMA, white matter abnormality; % agree, percentage agreement.

Evidence of predictive validity (Spittle 2008, Noble 2011)							
Assessment Tool	**Outcome assessment**	**Sample Characteristics**	**Age at outcome**	**Age at initial assessment**	**Sensitivity (%)**	**Specificity (%)**	**Correlations Pearson's r**
GMs	CP (n=19) or learning disability[c] (n=2)	Preterm infants (n=29)	12-36mo	26-62wks PMA	100	59.1	n/a
	CP or DQ<85 (n=60)	Preterm and term infants (n=130)	24mo	46-60wks PMA	95	96	n/a
	CP or DQ<85 (n=18)	Term infants (n=58)	24mo	38-42wks PMA	94	59	n/a
				43-47wks PMA		86	
				48-56wks PMA		83	
	CP or DQ<85 (n=31)	Preterm infants (n=65)	24mo	28-37wks PMA	90.6	57.6	n/a
				38-42wks PMA	100	64.5	
				43-65wks PMA	96.2-100	74.2-98.8	
	CP or DQ<85 (n=11)	IUGR and term control (n=62)	24mo	Term	83.33	80	n/a
				49-51wks PMA	100[a]	100[a]	
				54-56wks PMA	100[a]	93.0[a]	
	AIMS, NSMDA, CP (n=5)	Preterm infants (n=86)	12mo	1mo	82.8 AIMS (NPV=84.4)	48.2 AIMS (PPV=45.3)	0.31 0.24
					86.7 NSMDA (NPV=93.8)	42.9 NSMDA (PPV=24.5)	0.2

					100.0 CP (NPV=100)	40.0 CP (PPV=9.4)	
				3mo	40.0 AIMS (NPV=72.3)	85.5 AIMS (PPV=60.0)	0.27
					62.5 NSMDA (NPV=90.8)	85.5 NSMDA (PPV=50.0)	0.42 0.47
					100.0 CP (NPV=100.0)	81.3 CP (PPV=0.3)	
Dubowitz	MRI (WMA/GMA)	VLBW preterm infants (n=66)	4mo CA	Term	88 (NPV=92)	46 (PPV=34)	n/a
	INFANIB	Preterm infants BW<1250g (n=47)	12mo CA	Term	n/a	n/a	Total factor scores F92.42=8.7; p<0.001;R^2=0.71
	Amiel-Tison Milani-Comparetti Examination of motor development BSITD II	Low risk infants BW >1000g (n=100)	12mo CA	30-33wks gestation	2 + deviant signs; 91 (NPV=92)	2 + deviant signs; 79 (PPV=76)	r=0.7602 (p<0.001) with neurodevelop mental outcome
				34-36wks gestation	4 + deviant signs; 55 (NPV=74)	4 + deviant signs; 97 (PPV=92)	
				37-40wks gestation			

TIMP	AIMS scores<5th centile (n=16) at 6mo	Preterm and term infants (n=96)	6mo	32wks PMA – 4moCA (z-score-0.5SD)[b]	62.5	77.4	0.37-0.67
	(n=14) at 9mo		9mo		91.7	75.7	0.20-0.56 (AIMS centile)
	(n=12) at 12mo		12mo		45-92	68-78	0.32-0.55(AIMS centile)
	BOTMP (motor delay) (n=8)	Preterm and term infants (n=35)	4y9mo	32wks PMA – 4mo CA (z-score 1.6SD) [b]	50	100	0.36 (BOTMP score)
	Gross motor delay (PDMS DQ>70) (n=12)	Preterm and term infants (n=61)	4-5y	1mo (z-score 0.5SD) [b]	33	94	0.43 (PDMS GMQ)
					50	86	
				2mo (z-score 0.5SD) [b]	72	91	0.42(PDMS GMQ)
				3mo (z-score 0.5SD) [b]			0.65(PDMS GMQ)
BSITD III	n/s		n/s	n/s	n/s	n/s	n/s
AIMS	Paediatrician classification of normal/suspicious (n=142) vs. abnormal development (n=22)	Preterm and term infants (n=164)	18mo	4mo (10th centile)[b]	77.3	81.7	
				8mo (5th centile)[b]	86.4	93.0	
	BSID-II PDI	Preterm infants (n=41)	12mo	6mo	n/s	n/s	0.56 (BSID-II PDI)

NSMDA	Paediatrician classification of development	Low-birthweight infants (n=148)	24mo	1mo (25% below average)[b]	68.8*	72.6	n/s
				4mo (25% below average)[b]	80.0	56.9	n/s
				8mo (25% below average)[b]	82.4	83.7	n/s
				12mo (25% below average)[b]	58.8	93.3	n/s

[a]Abnormal and absent fidgety movements were combined; [b]Cut-off score for typical versus atypical motor development; [c]US usage: mental retardation; AIMS, Alberta Infant Motor Scale; BOTMP, Bruininks-Oseretsky Test of Motor Proficiency; BTSID III, Bayley Scales of Infant and Toddler Development; BW, birth weight; CA, corrected age; DQ, Developmental Quotient; Dubowitz, The Neurological Assessment of the Preterm and Full-term Newborn Infant; GMA, grey matter abnormality; GMQ, Gross Motor Quotient; GMs, General Movements Assessment; INFANIB, Infant Neurological International Battery; IUGR, intrauterine growth retardation; MRI, magnetic resonance imaging; NNNS, Neonatal Intensive Care Network Neurobehavioural Scale; NPV, negative predictive value; NSMDA, Neuro Sensory Motor Development Assessment; n/a, not available; n/s, no study identified; PDI, Psychomotor Development Index; PDMS, Peabody Developmental Motor Scale; PMA, postmenstrual age; PPV, positive predictive value; r, Pearson's correlation coefficient; TIMP, Test of Infant Motor Performance; VLBW, Very low birth weight; WMA, white matter abnormality.

sensitivity – the percent of correctly identified CP cases; specificity – the percent of correctly identified non-CP cases; positive predictive value (PPV) – the percent of true CP out of all identified positive cases; negative predictive value (NPV) – the percent of true non-CP out of all identified negative cases; accuracy – the percent of true positives and negatives out of all infants tested.

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