Early reach to grasp development of infants with asymmetric brain injury on the Grasp and Reach Assessment of Brisbane (GRAB)

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Master of Occupational Therapy Studies, Bachelor of Science (Biomedical Science)

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School of Medicine
Abstract

Background

One to two of every 1000 infants have an asymmetric brain injury (asymBI; brain lesions as a result of arterial stroke or venous infarction, occurring unilaterally or bilaterally with more involvement on one side of the brain). Infants with asymBI are at risk for developing Unilateral Cerebral Palsy (UCP) by 12 months of age. Based on CP Register reports, UCP accounts for 38% of children diagnosed with CP in Australia. Unilateral upper limb (UL) impairment results in difficulty exploring objects and impaired development of UL motor skills. Asymmetric UL motor development in infants with stroke who are younger than 12 months corrected age (C.A.) is an important marker of an emerging hemiparesis. A few studies have compared the early development of reach to grasp behaviours in preterm infants or infants with stroke to healthy infants younger than 12 months C.A. There is limited use, however, of valid and reliable measures to accurately detect UCP in infants with asymBI. There is a growing body of evidence to support non-surgical UL interventions for school-aged children with UCP, however, the efficacy of interventions for infants at risk of UCP is unclear.

Aims

The aims of this doctoral program were to: (1) determine the efficacy of non-surgical UL interventions on UL motor function (including self-care) in infants with asymBI; (2) develop a quantitative measure to detect asymmetries in the development of early reach to grasp in infants with asymBI, the Grasp and Reach Assessment of Brisbane (GRAB), and evaluate its construct validity and internal consistency; (3) evaluate intra- and inter-rater reproducibility of the GRAB; and (4) examine longitudinal development of reach to grasp at 14, 16 and 18 weeks C.A. on the GRAB, to predict delayed motor development at 6 and 12 months C.A. on the Bayley Scales of Infant and Toddler Development (BSID III) in infants with asymBI, compared to healthy infants.

Research design

Aim 1 was addressed by undertaking a systematic review (SR). Aim 2 was addressed by developing the GRAB as a quantitative measure to detect asymmetries between ULs in early reach and grasp behaviours in infants with asymBI, and performing a validity study; and Aim 3 was addressed by performing a reproducibility study. Aim 4 was addressed by undertaking a longitudinal study that examined early reach and grasp behaviours between infants with asymBI and healthy infants on the GRAB; and evaluated
the relationship between early reach to grasp development on the GRAB and motor development on the BSID III.

**Results**

The SR identified that modified constraint induced movement therapy (mCIMT), hybrid CIMT and occupational therapy (OT) supplemented with intramuscular UL injections of Botulinum toxin A (BoNT-A) are more effective than usual care at improving unimanual and bimanual UL motor function. These interventions may benefit infants with asymBI when they are based on motor learning theory, involve goal-directed training and are delivered in a variety of environments, including the home.

The GRAB demonstrated evidence of: (i) moderate to strong construct validity; (ii) strong internal consistency; (iii) strong intra- and inter-rater reliability; and (iv) strong intra- and inter-rater agreement as a quantitative research measure for detecting and evaluating early unimanual and bimanual reach and grasp behaviours both in infants with asymBI and healthy infants. Infants with asymBI were less likely to demonstrate unimanual reaching; demonstrated a paucity of unimanual and bimanual grasping; and scored lower on the BSID III Motor Scale compared to healthy infants. The GRAB detected asymmetries in unimanual reaching and grasping from 14 to 18 weeks C.A. in infants with asymBI. The number of unimanual contacts, grasps and bimanual grasps at 18 weeks C.A. on the GRAB were strong predictors of FM development on the BSID III for infants with asymBI only at six months C.A. The BSID III underestimated FM impairment in infants with clinical signs of hemiplegia at six and 12 months C.A.

**Conclusions**

This doctoral program has identified that there is limited evidence supporting the efficacy of UL interventions for infants with asymBI. Another important finding of this research is that there is limited evidence for valid and reliable measures in this very young and at-risk population to: (i) accurately detect and/or predict UCP by quantifying and evaluating early abnormalities in UL motor development; and (ii) examine the efficacy of interventions and quantify meaningful change in UL motor function in response to interventions.

The GRAB provides an important contribution as a new research measure to detect, quantify and evaluate early reach to grasp development in infants with asymBI; and to predict FM development at six months C.A. on the BSID III. The GRAB detected asymmetric unimanual reach to grasp development in infants with asymBI. Compared to healthy infants, however, infants with asymBI demonstrated a paucity rather than
asymmetry of unimanual grasping. Further work is required to investigate the relationship of the GRAB with other validated measures of reach and grasp development, such as the Hand Assessment of Infants (HAI); and to evaluate its clinical utility.
Declaration by author

This thesis is composed of my original work, and contains no material previously published or written by another person except where due reference has been made in the text. I have clearly stated the contribution by others to jointly-authored works that I have included in my thesis.

I have clearly stated the contribution of others to my thesis as a whole, including statistical assistance, survey design, data analysis, significant technical procedures, professional editorial advice, and any other original research work used or reported in my thesis. The content of my thesis is the result of work I have carried out since the commencement of my research higher degree candidature and does not include a substantial part of work that has been submitted to qualify for the award of any other degree or diploma in any university or other tertiary institution. I have clearly stated which parts of my thesis, if any, have been submitted to qualify for another award.

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Micah Perez
Publications during Candidature

Peer-reviewed publications


Publications included in this thesis (by chapter)


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Contributions by others to the thesis

Principal advisor: Professor Roslyn Boyd
Associate advisor: Professor Jenny Ziviani
Associate advisor: Dr Andrea Guzzetta

Conception and design of overall study:
Roslyn Boyd, Andrea Guzzetta, Jenny Ziviani were chief investigators on the overall study grant for the UPper limb Baby Early Action-observation Training (UP-BEAT) Study, which was funded by the Australian Research Council (DP110104292). The UP-BEAT Study comprised two parallel randomised controlled trials investigating the efficacy of Action Observation Training in infants with asymmetric brain injury and healthy infants; compared to standard Toy Observation Training (a sham control intervention). The chief investigators conceptualized the study design and selected the primary and secondary outcome measures.

Ethical conduct of overall study:
Roslyn Boyd, Andrea Guzzetta, Jenny Ziviani and Micah Perez were responsible for obtaining ethical approval for the study and for ethical reporting of outcomes.

Conduct of project for the study in south-east Queensland:
Kerry Provan, Joanne Bowden and Bernadette Shannon (occupational therapists) were responsible for study coordination. Micah Perez (Candidate and occupational therapist), Kerry Provan and Lisa Findlay (occupational therapists) were responsible for recruitment of participants. Lisa Findlay and Imogen Fisher were responsible for the piloting phase of the project. Kerry Provan and Lisa Findlay designed the study documents, including the intervention handouts and flyers. Micah Perez designed the study referral flyer that was given to medical staff and clinicians who assisted with recruitment of infants with asymmetric brain lesions. Kerry Provan, Bernadette Shannon and Micah Perez were responsible for collecting initial and follow-up medical history information from families, medical records and treating clinicians for infants with asymmetric brain lesions. Lisa Findlay and Micah Perez were responsible for delivering the intervention and providing training to participants’ parents and/or caregivers. Micah Perez, Kerry Provan, Lisa Findlay, Imogen Fisher, Joanne Bowden and Bernadette Shannon (occupational therapists) and Christine Finn (physiotherapist) were responsible for conducting
Micah Perez was responsible for scoring the Grasp and Reach Assessment of Brisbane (GRAB).

**Conduct of project for the concurrent study in Italy:**
Andrea Guzzetta (child neurologist) was responsible for study coordination. Valentina Burzi, Giada Sgherri (medical doctors) and Gessica Tealdi (physiotherapist) were responsible for recruitment of participants and conducting assessments and home visits. Valentina Burzi was responsible for scoring the BSID III. Micah Perez was responsible for scoring the GRAB.

**Development and validation of the Grasp and Reach Assessment of Brisbane (GRAB):**
The GRAB was developed by Micah Perez, Andrea Guzzetta, Roslyn Boyd, Jenny Ziviani, Kerry Provan, Lisa Findlay and Imogen Fisher. Pilot testing of the scoring method was undertaken by Micah Perez, Andrea Guzzetta, Kerry Provan, Lisa Findlay and Imogen Fisher. Development of the scoring criteria and revisions of the scoring method were undertaken by Micah Perez, Andrea Guzzetta, Valentina Burzi and Giada Sgherri. Micah Perez was responsible for: (i) reporting the development of the GRAB; (ii) evaluating and reporting its construct validity, internal consistency, intra-rater and inter-rater reproducibility; and (iii) evaluating and reporting longitudinal reach to grasp development of infants with asymmetric brain lesions measured on the GRAB, in relation to prediction of delayed fine motor (FM) development on the BSID III FM subtest compared to healthy infants; under the supervision of Roslyn Boyd, Jenny Ziviani and Andrea Guzzetta. Inter-rater reproducibility of the measurements on the GRAB was established by Micah Perez and Giada Sgherri, with guidance from Roslyn Boyd, Jenny Ziviani and Andrea Guzzetta. Biostatistical advice was provided by Robert Ware for analysing the internal consistency, intra-rater and inter-rater reproducibility of the measurements on the GRAB; and for examining longitudinal reach to grasp development on the GRAB in relation to prediction of FM development on the BSID III in both infants with asymBI and healthy infants.

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Statement of parts of the thesis submitted to qualify for the award of another degree

None.
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<td>ADLs</td>
<td>Activities of Daily Living</td>
</tr>
<tr>
<td>AEIs</td>
<td>Adverse Events</td>
</tr>
<tr>
<td>AHA</td>
<td>Assisting Hand Assessment</td>
</tr>
<tr>
<td>AI</td>
<td>Asymmetry Index</td>
</tr>
<tr>
<td>AIP</td>
<td>Anterior Intraparietal area</td>
</tr>
<tr>
<td>AOT</td>
<td>Action Observation Training</td>
</tr>
<tr>
<td>ARC</td>
<td>Australian Research Council</td>
</tr>
<tr>
<td>asymBI</td>
<td>asymmetric Brain Injury</td>
</tr>
<tr>
<td>BBT</td>
<td>Box and Block Test</td>
</tr>
<tr>
<td>BiT</td>
<td>Bimanual task-specific Training</td>
</tr>
<tr>
<td>BoNT-A</td>
<td>Botulinum toxin A</td>
</tr>
<tr>
<td>BOT</td>
<td>Bimanual Occupational Therapy</td>
</tr>
<tr>
<td>BSID II</td>
<td>Bayley Scales of Infant and Toddler Development (version II)</td>
</tr>
<tr>
<td>BSID III</td>
<td>Bayley Scales of Infant and Toddler Development (version III)</td>
</tr>
<tr>
<td>BT</td>
<td>Bimanual Training</td>
</tr>
<tr>
<td>C.A.</td>
<td>Corrected Age</td>
</tr>
<tr>
<td>CH</td>
<td>Congenital Hemiplegia</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence Interval</td>
</tr>
<tr>
<td>CIMT</td>
<td>signature Constraint Induced Movement Therapy</td>
</tr>
<tr>
<td>CP</td>
<td>Cerebral Palsy</td>
</tr>
<tr>
<td>CS</td>
<td>Corticospinal</td>
</tr>
<tr>
<td>DD</td>
<td>Developmental disabilities</td>
</tr>
<tr>
<td>Deff</td>
<td>Design effect</td>
</tr>
<tr>
<td>eco-CIMT</td>
<td>ecological approach of Constraint Induced Movement Therapy</td>
</tr>
<tr>
<td>EDPA</td>
<td>Erhardt Developmental Prehension Assessment</td>
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<tr>
<td>EE</td>
<td>Environmental Enrichment</td>
</tr>
<tr>
<td>ES</td>
<td>Effect Size</td>
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<tr>
<td>FES</td>
<td>Functional Electrical Stimulation</td>
</tr>
<tr>
<td>FM</td>
<td>Fine Motor</td>
</tr>
<tr>
<td>fMRI</td>
<td>functional Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>F5</td>
<td>Premotor area in the brain of macaque monkeys containing mirror neurons</td>
</tr>
<tr>
<td>FUT</td>
<td>Forced Used Therapy</td>
</tr>
<tr>
<td>GA</td>
<td>Gestational Age</td>
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<tr>
<td>GM</td>
<td>Gross Motor</td>
</tr>
<tr>
<td>GMs</td>
<td>Prechtl's method on the qualitative assessment of General Movements</td>
</tr>
<tr>
<td>GRAB</td>
<td>Grasp and Reach Assessment of Brisbane</td>
</tr>
<tr>
<td>HABIT</td>
<td>Hand-arm Bimanual Intensive Therapy</td>
</tr>
<tr>
<td>HAI</td>
<td>Hand Assessment of Infants</td>
</tr>
<tr>
<td>hybrid CIMT</td>
<td>modified CIMT combined with bimanual training and/or a 'transfer package' of therapy</td>
</tr>
<tr>
<td>I</td>
<td>Impaired limb</td>
</tr>
<tr>
<td>ICC</td>
<td>Intraclass Correlation Coefficient</td>
</tr>
<tr>
<td>INMAP</td>
<td>Inventory of New Motor Activities and Programs instrument</td>
</tr>
<tr>
<td>IRP</td>
<td>Intensive Rehabilitation Program</td>
</tr>
<tr>
<td>IRR</td>
<td>Incidence Rate Ratio</td>
</tr>
<tr>
<td>IVH</td>
<td>Intraventricular haemorrhage</td>
</tr>
<tr>
<td>Kg/bw</td>
<td>Kilograms per body weight</td>
</tr>
<tr>
<td>L</td>
<td>Left limb</td>
</tr>
<tr>
<td>LoA</td>
<td>Limits of Agreement</td>
</tr>
<tr>
<td>mCIMT</td>
<td>modified Constraint Induced Movement Therapy</td>
</tr>
<tr>
<td>MD</td>
<td>Mean Difference</td>
</tr>
<tr>
<td>mini-AHA</td>
<td>mini-Assisting Hand Assessment</td>
</tr>
<tr>
<td>MMA</td>
<td>Modified Melbourne Assessment</td>
</tr>
<tr>
<td>MNS</td>
<td>Mirror Neuron System</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>MUUL</td>
<td>Melbourne Assessment of Unilateral Upper Limb Function</td>
</tr>
<tr>
<td>NDT</td>
<td>Neurodevelopmental Treatment</td>
</tr>
<tr>
<td>NS</td>
<td>Not Significant</td>
</tr>
<tr>
<td>OT</td>
<td>Occupational Therapy</td>
</tr>
<tr>
<td>PAFT</td>
<td>Pediatric Arm Function Test</td>
</tr>
<tr>
<td>PDMS-FM</td>
<td>Peabody Developmental Motor Scales (Fine Motor subscale)</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>PEDI</td>
<td>Pediatric Evaluation of Disability Inventory</td>
</tr>
<tr>
<td>PF</td>
<td>Inferior parietal lobule in the brain of macaque monkeys</td>
</tr>
<tr>
<td>PMAL</td>
<td>Pediatric Motor Activity Log</td>
</tr>
<tr>
<td>PMAL-R</td>
<td>Pediatric Motor Activity Log (revised version)</td>
</tr>
<tr>
<td>PT</td>
<td>Physiotherapy</td>
</tr>
<tr>
<td>PVL</td>
<td>Periventricular leukomalacia</td>
</tr>
<tr>
<td>QUEST</td>
<td>Quality of Upper Extremity Skills Test</td>
</tr>
<tr>
<td>r</td>
<td>Regression coefficient</td>
</tr>
<tr>
<td>R</td>
<td>Right limb</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomised Controlled Trial</td>
</tr>
<tr>
<td>SCPE</td>
<td>Surveillance of Cerebral Palsy in Europe</td>
</tr>
<tr>
<td>SD</td>
<td>Standard Deviation</td>
</tr>
<tr>
<td>SDD</td>
<td>Smallest Detectable Difference</td>
</tr>
<tr>
<td>SEM</td>
<td>Standard Error of Measurement</td>
</tr>
<tr>
<td>SM</td>
<td>Sensorimotor</td>
</tr>
<tr>
<td>SMA</td>
<td>Supplementary Motor Area</td>
</tr>
<tr>
<td>SMD</td>
<td>Standardised Mean Difference</td>
</tr>
<tr>
<td>SR</td>
<td>Systematic Review</td>
</tr>
<tr>
<td>TCP</td>
<td>Toy Colour Phase</td>
</tr>
<tr>
<td>TMS</td>
<td>Transcranial Magnetic Stimulation</td>
</tr>
<tr>
<td>TP</td>
<td>Time Phase</td>
</tr>
<tr>
<td>U</td>
<td>Unimpaired limb</td>
</tr>
<tr>
<td>UCP</td>
<td>Unilateral Cerebral Palsy</td>
</tr>
<tr>
<td>UL</td>
<td>Upper limb</td>
</tr>
<tr>
<td>UP-BEAT</td>
<td>Upper limb Baby Early Action-observation Training</td>
</tr>
<tr>
<td>VA</td>
<td>Visual Attention</td>
</tr>
<tr>
<td>WeeFIM</td>
<td>Paediatric version of the Functional Independence Measure</td>
</tr>
<tr>
<td>WPPS III</td>
<td>Wechsler Preschool and Primary Scale of intelligence (third edition)</td>
</tr>
<tr>
<td>95% CI</td>
<td>Ninety five percent Confidence Interval</td>
</tr>
</tbody>
</table>
Glossary of operational definitions for terms used in the thesis

Assisting Hand Assessment (AHA)  
The AHA was designed to examine the use of the impaired UL during bimanual tasks in children with uCP or obstetric brachial plexus palsy (OBPP), aged 18 months to 12 years. The AHA involves a video-recorded, structured play session whereby toys (designed to elicit bimanual UL use) are provided to children. The AHA comprises 22 test items which are scored on a four-point rating scale, and from which raw scores are converted into logit scores (ranging from 0 to 100). The AHA is a valid measure for children with uCP and OBPP between 18 months to 12 years, has demonstrated excellent intra- and inter-rater reliability.\textsuperscript{1,2} The AHA has also demonstrated responsiveness to change following mCIMT.\textsuperscript{3}

Asymmetric brain injury (asymBI)  
Brain lesions as a result of arterial stroke or venous infarction occurring on one side (i.e. unilateral brain lesion) or more involved on one side of the brain (i.e. asymmetric bilateral brain lesion). Participants in the asymBI group, whether they were preterm or term-born infants, had unilateral (one-sided) or asymmetric bilateral (more involved on one side) brain lesions. The most common brain lesions identified in the asymBI group in this study were: stroke, intraventricular haemorrhage (IVH), and periventricular leukomalacia (PVL).

Design Effect (Deff)  
The Deff is the amount that a sample size needs to be multiplied in a study that involves cluster sampling.\textsuperscript{4} An equivalent sample size can then be calculated, which reflects the amount of data that is contributed by each infant, based on the total number of toy presentations and the Deff.\textsuperscript{4} The Deff was calculated for evaluation of internal consistency and reproducibility of measurements on the GRAB. For example, for internal consistency, one cluster
contains a total possible six toy presentations for each infant. The Deff was calculated using the formula: \( \text{Deff} = 1 + (n' - 1) \times ICC \); whereby \( \text{Deff} \) refers to the design effect, \( n' \) refers to the average cluster size, and \( ICC \) refers to the intraclass correlation coefficient. The equivalent sample sizes for each behavioural event (i.e. number of unimanual contacts, unimanual grasps and bimanual grasps) were calculated using the following formula: total number of toy presentations / \( \text{Deff} \).

Ecological approach of Constraint Induced Movement Therapy (eco-CIMT)

Constraint Induced Movement Therapy is performed in the child’s usual environment(s), such as the home and/or school; and is delivered by parents and/or teachers on a daily basis, with therapist supervision once per week.\(^5\)

Environmental Enrichment (EE)

Enriching the environment to provide a child with opportunities for motor learning through different modalities such as active motor training, parental education and environmental adaptation.\(^6\)\(^8\)

Grasp

Grasp involves contacting the toy using all or most fingers with the palm, and closing around the toy (or holding the toy). Grasping may be brief or the toy may be held for a prolonged period of time. The infant may also adjust his/her grasp around the toy; and/or manipulate the toy with finer movements around the toy’s head/arms/hands.

Hand Assessment of Infants (HAI)

The HAI is currently being developed for infants with asymBI, aged three to 12 months, to: (i) examine the quality of goal-directed unimanual and bimanual actions during play; and (ii) detect asymmetries between ULs.\(^9\)\(^10\)

The HAI involves a video-recorded, semi-structured play session whereby toys (designed to elicit goal-directed unimanual and bimanual UL use) are provided to
The preliminary scale of the HAI comprises 18 items which are scored on a three-point rating scale. Each UL is scored separately on the HAI to reflect potential asymmetries between ULs, and both ULs are scored together to reflect bimanual UL use based on criterion and norm-reference scales. A preliminary Rasch analysis suggests promising results for validity of the HAI; however, intra-, inter-rater and test-retest reproducibility of the HAI are yet to be established.

Mini-Assisting Hand Assessment (mini-AHA)

The mini-AHA is currently the only valid measure reported for infants confirmed with congenital hemiplegia, aged eight to 18 months, to examine the use of their impaired UL during bimanual tasks. The mini-AHA is based on the Assisting Hand Assessment (AHA; for children with uCP and obstetric brachial plexus palsy, aged 18 months to 12 years), and involves a video-recorded, semi-structured play session whereby toys (designed to elicit bimanual UL use) are provided to infants. The mini-AHA involves a video-recorded, semi-structured play session whereby toys (designed to elicit bimanual UL use) are provided to infants. The mini-AHA comprises 20 test items which are scored on a four-point rating scale, and from which raw scores are converted into logit scores (ranging from 0 to 100). Intra- and inter-rater reproducibility of the mini-AHA, however, are yet to be established.

Modified Constraint Induced Movement Therapy (mCIMT)

Constraint Induced Movement Therapy that was modified for a paediatric population with unilateral Cerebral Palsy. It involves alternative restraint wear to casting with unimanual training and/or a home program.

Modified Melbourne Assessment (MMA)

The MMA is a modified version of the Melbourne Assessment of Unilateral Upper Limb Function, designed
to measure quality of unilateral UL movement in children with neurological impairment (including CP), aged two to four years. The MMA is able to discriminate between mild, moderate and severe levels of UL impairment based on clinicians’ ratings of severity of unilateral UL impairment. It has strong concurrent validity with the Quality of Upper Extremity Skills Test (QUEST).\textsuperscript{14}

Reach

Arm movements made towards the toy in an attempt to contact the toy (including swiping) during the transport phase, without contacting the toy.

Signature Constraint Induced Movement Therapy (CIMT)

Constraint Induced Movement Therapy that was originally tested in an adult population with chronic stroke and an UL hemiparesis. It involves extended periods of restraint wear (approximately 20 hours per day over 14 days) with casting,\textsuperscript{15} and accompanied by shaping (which is a behavioural training technique that involves operant conditioning of movements of the impaired UL and motor recovery is achieved in small, successive steps).\textsuperscript{16,17}
Chapter 1: Introduction, thesis plan and aims

1.1. Introduction

Healthy infants use their upper limbs (ULs) to explore and make sense of objects in their immediate environment. Being able to explore objects enables infants to start learning how to play and interact with their surroundings. Early spontaneous movements mature into purposeful reaching, grasping, manipulating and releasing. These skills form the foundation to perform more complex daily tasks such as eating, dressing, toileting and grooming. In contrast, infants with asymmetric brain injury (asymBI; brain lesions as a result of arterial stroke or venous infarction occurring on one side or more involved on one side of the brain) may have an impaired ability to spontaneously explore objects and engage in their environment. This can consequently impact their ability to develop the foundational UL motor skills necessary for object exploration and play.

In order to understand how asymBI may lead to impaired UL motor development, an understanding of typical UL motor development must first be established. To this end, the critical periods of typical UL motor development and the neural correlates underlying the development of UL motor skills will initially be presented in this chapter. The impact of asymBI on UL motor development will then be examined. The critical window for early detection of unilateral Cerebral Palsy (UCP) and early UL interventions will then be discussed. Following this, the Mirror Neuron System (MNS) will be introduced, which is believed to underlie our ability to observe, understand and imitate another’s actions. This system will then be discussed in relation to action observation and imitation. Following this, the concept of cortical reorganisation occurring after asymBI will be discussed. Action Observation Training (AOT) will then be reviewed as a new rehabilitative approach for infants with asymBI, which is theoretically based on the MNS and involves imitation of UL actions. Following this, Aim 1 will be initially addressed by summarising the first paper in this thesis, a book chapter entitled “Very early upper limb interventions for infants with asymmetric brain lesions” (the full chapter is provided as Appendix 9.1.). Finally, the plan and format of this thesis will be presented; followed by the aims and hypotheses of this doctoral program.

1.1.1. Critical periods of typical upper limb motor development

Upper limb skills of healthy infants generally develop in several stages: i) discovering the hand; ii) visually regarding the hand; iii) visually exploring objects in space; iv) swiping at objects; v) contacting objects; vi) ineffectively grasping objects; and
vii) developing prehensile movements to better grasp objects. These stages are not consecutive and often overlap.

Infants begin to discover their hands by bringing their hands to their mouth and face, as well as exploring their fingers and hands, prior to the development of prehension of objects. Prior to the onset of prehension (i.e. the action comprised of reaching and grasping movements), infants demonstrate prehensile movements, which reflect spontaneous, oscillatory UL movements that will eventually mature into prehension. Prehensile movements provide infants with multimodal input about their UL function within their environment, and provide sensorimotor (SM) experiences that can help them to learn how to control their ULs in preparation for controlled, goal-directed movements. Examples of prehensile movements include increased midline arm movements (such as bringing the hand to the face or mouth), increased “forward” arm movements whilst visually regarding a toy, more frequent arm movements towards a toy, and faster or slower arm movements directed towards a toy.

Reaching involves sequential UL movements directed towards an object, changes in movement velocity (i.e. accelerations and decelerations), and adjustments to wrist and hand orientation (i.e. pre-shaping of the hand) whilst moving towards an object, in preparation for contacting or grasping an object. Finger movements observed within the first few weeks of life may be the result of a grasp reflex, which will later mature into grasping. Grasping involves the shaping and coordinated movements of fingers and rotation of the wrist in a manner that anticipates the size, shape and physical features of the target object. The force of the grasp is applied when the object is contacted, in order to grasp and lift the object.

As soon as infants can voluntarily grasp, (usually at around three months of age) they may begin to demonstrate laterality or hand preference, however, they may switch from left to right depending on their ability to predict and perform a reaching strategy to successfully grasp a toy. In studies examining simple grasping of objects in infants, laterality or hand preference does not appear to be strong initially and often varies between right, left and no preference. Switching hands while manipulating an object happens early in motor development, prior to six months of age. Clear hand preference in toddlers (18 months) can be observed when they undertake bimanual tasks. When infants are given an object, they tend to prehend it with the hand closer to, or on the same side (i.e. ipsilateral hand), as the object. If the infant is unable to reach for an
object quickly enough with the ipsilateral hand, the infant may cross the midline or attempt to grasp the object with his/her other (i.e. contralateral) hand.\textsuperscript{41,42}

In the first year of life, after developing controlled and purposeful unilateral reaching strategies to successfully grasp and retrieve objects, infants have been reported to: (i) demonstrate laterality between ULs, switch hand preference and demonstrate unilateral reaching following the onset of crawling (which requires uncoupling of the ULs and interlimb coordination)\textsuperscript{43}; and (ii) resume bilateral reaching following the onset of walking\textsuperscript{44}; and (iii) demonstrate unilateral reaching once stable gait and balance control were achieved.\textsuperscript{44} The emergence of new motor skills, such as crawling and walking, may impact on previously established motor patterns, such as unilateral reaching, since these skills rely on postural control and involve postural changes.\textsuperscript{44} In addition, changes in previously established reaching patterns may reflect neuromotor reorganisation and integration of new motor skills into existing cognitive and motor patterns.\textsuperscript{43,44} This important work by Corbetta and colleagues\textsuperscript{43,44} demonstrates that crawling and walking are iterative processes that can influence reach and grasp development; and that changes in primary reaching patterns can be influenced by experience.

There is evidence that fine motor (FM) skills such as reaching, grasping and releasing develop chronologically. The timing of these events is presented in Table 1.1. In reality, these proposed time points are variable and often overlap during early upper limb motor development.

1.1.2. Neural correlates underlying the development of upper limb motor skills

The parietal cortex has a role in monitoring and correcting reaching movements.\textsuperscript{33} It sends signals to the frontal cortex, which may play a part in the coordination of reaching.\textsuperscript{33} The premotor and motor cortices code for the direction of reaching movements; the neurons of the motor cortex specifically code for proprioceptive movements.\textsuperscript{33} Each set of neurons that code for reaching in a particular direction requires visual input about the target location, and proprioceptive input on the position of the arm in space.\textsuperscript{33} The supplementary motor area (SMA) appears to be involved in coding for bimanual reaching movements with a specific visual target.\textsuperscript{33} The parietal, premotor and motor cortices work together to enable an individual to reach in the intended direction of a visual target.\textsuperscript{33} The neurons of the premotor (including the SMA) and motor cortices have a specific role for initiating goal-directed movements, while the parietal cortical neurons have a role in monitoring executed movements.\textsuperscript{33}
The type of grasp used to contact an object is the result of a pre-existing motor sequence, as well as the ability to adapt and respond to new demands.\textsuperscript{33} The neural coding of grasping movements of an individual can be task-dependent and not always organised in a somatotopic way (i.e. dependent on a specific area of the brain). This implies that cortical activation can differ depending on the anticipated grasp pattern.\textsuperscript{33} The ‘visual dominant’ neurons of the parietal cortex are involved in processing the visual input received from the target object. These neurons then send a signal to the premotor cortex neurons to prepare another signal to grasp the object. The grasp command signal from the premotor cortex neurons is then sent back to the parietal ‘motor dominant’ neurons, which becomes the visuomotor signal that is sent back to the premotor neurons.\textsuperscript{33,45}

**Table 1.1. Development of reaching, grasping and releasing**

<table>
<thead>
<tr>
<th>General Fine Motor Skill</th>
<th>Specific Fine Motor Skill</th>
<th>Proposed Age (post-term months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reaching</td>
<td>Visually attending to objects carefully while reaching ineffectively</td>
<td>1 to 3 months</td>
</tr>
<tr>
<td></td>
<td>Demonstrating finger, eye and hand adjustments to better contact objects</td>
<td>4 months</td>
</tr>
<tr>
<td></td>
<td>Reaching objects in a controlled manner</td>
<td>6 months</td>
</tr>
<tr>
<td>Grasping</td>
<td>Reflexively grasping objects</td>
<td>Birth until 4 months</td>
</tr>
<tr>
<td></td>
<td>Beginning to use a voluntary palmar grasp with both hands</td>
<td>3 months</td>
</tr>
<tr>
<td></td>
<td>Beginning to grasp with the preferred hand</td>
<td>5 months</td>
</tr>
<tr>
<td></td>
<td>Using a pincer grasp</td>
<td>9 months</td>
</tr>
<tr>
<td></td>
<td>Using a controlled grasp</td>
<td>14 months</td>
</tr>
<tr>
<td>Releasing</td>
<td>Having a basic ability to release objects from grasp</td>
<td>6 to 12 months</td>
</tr>
<tr>
<td></td>
<td>Demonstrating controlled release of objects</td>
<td>18 months</td>
</tr>
<tr>
<td>Bimanual coordination</td>
<td>Demonstrating reaching, grasping and releasing skills that are well-coordinated and controlled</td>
<td>18 months</td>
</tr>
</tbody>
</table>

References. (e.g. \textsuperscript{21,30,36,46-49})

Neurons which code for grasping objects were first recorded in primate models.\textsuperscript{50} In primate models, neurons associated with active hand manipulation have been found in the inferior parietal lobe\textsuperscript{51} and in the anterior intraparietal area (AIP), which is located in the rostral posterior intraparietal sulcus.\textsuperscript{45} The AIP is connected to the premotor cortex; and together with various areas within the premotor cortex, forms a visuomotor coding system for hand manipulation in primates.\textsuperscript{33} Area F5, located in the rostral inferior part of area 6 in the primate premotor cortex, contains specialised ‘grasping’ neurons, which fire when the primate grasps an object.\textsuperscript{52} Some grasping neurons fire when the primate intends to grasp an object and only stop firing when the object is grasped; some neurons fire when the primate’s fingers are preparing to grasp the object (i.e. fingers are extending...
and flexing prior to grasp); and some neurons fire when the primate has grasped the object (i.e. fingers are flexed around the object). These F5 neurons are highly selective; 85% of grasping neurons code for precision grip, finger prehension and whole-hand prehension; and there are different neurons which code for grasping different shaped objects (e.g. one set for grasping a ball, another set for grasping a tube).

1.1.3. Impact of asymmetric brain injury on upper limb motor development

There may be similarities in the impact of cortical neonatal lesions on the development of early UL motor skills between infant monkeys and humans. Experimental studies in primate models, which involved removing the pyramidal tract, revealed the role of the corticospinal (CS) tract in the control of finger movements. Removing the area of the CS tract which corresponded to the primate hand resulted in a neonatal lesion. The result of the lesion on the primates was an inability to acquire a precision grasp, which led to the primates being unable to pick up and manipulate small objects such as food pellets. In human infants, asymmetric brain lesions may frequently result from intraventricular haemorrhages (IVH) and periventricular leukomalacia (PVL), occurring on one side or being more involved on one side of the brain. The incidence of asymmetric brain lesions is less prevalent than bilateral lesions, occurring between one and two in every 1000 live births, based on studies conducted in the United States. Human infants with asymmetric brain lesions are at high risk of congenital hemiplegia by the end of their first year of life. These at-risk infants can experience impaired motor function (e.g. in the UL), which can detrimentally impact their ability to acquire manual skills needed to participate in daily activities (e.g. feeding and playing).

Unilateral CP is the most common type of CP, with a prevalence of one in 1300 live births. It is usually associated with a stroke (e.g. IVH) or an ischaemic lesion (e.g. PVL), and can also be associated with a malformation and/or lack of cortical maturation in one hemisphere. These abnormalities in the brain often result in spasticity of the limbs on one side of the body. The presentation of hemiplegia (i.e. non-use of the impaired hand during activities which normally require bimanual hand use) is usually noticeable around ten months (40 weeks post-term) of age, which is the time when the hand is normally involved in prehension. Asymmetries in hand prehension skills (unimanual capacity, reaching and grasping) may be evident in infants with asymmetric brain lesions by six to twelve months corrected age (C.A.). Congenital hemiplegia refers to unilateral motor impairment as a result of presumed prenatal, perinatal or postnatal brain injury. Infants born prematurely may also sustain asymBI, which in and of itself, exposes the
immature brain to the risk of haemorrhage, or to transient or genetic coagulation. Most of these infants later develop mild or severe congenital hemiplegia. Perinatal brain lesions are most likely to be captured on magnetic resonance imaging (MRI) within the first two weeks after birth. Lesions which involve the basal ganglia and thalamus result in CP, and the severity of these lesions influence the severity of motor impairment.

Theoretically it is acknowledged that early intervention for infants at risk of developing congenital hemiplegia is important. The reality is that standard rehabilitation programs generally do not commence until six months of age. This may be due to infants not having a clear diagnosis of hemiplegia prior to this age; infants not being identified as being at risk of developing hemiplegia; and/or difficulties accurately predicting later hemiplegia based on presenting clinical signs. By six to twelve months of age, important phases of brain reorganisation may have already occurred for reach and grasp.

Examples of brain reorganisation occurring after perinatal stroke include: (i) retraction of the contralateral CS pathways between the damaged cortex and the impaired UL; and (ii) the synaptic space that was initially occupied by the contralateral CS pathways being replaced by the ipsilateral CS pathways between the intact cortex and the impaired UL. This type of reorganisation is only useful if there is some preservation of the contralateral CS pathways. When the lesion occurs later in pregnancy (e.g. later third trimester), the efficacy of this reorganisation becomes limited. The abnormal ipsilateral CS pathways can no longer effectively connect to the cortical and subcortical areas which are responsible for motor control. This reorganisation does not necessarily result in improvement of UL motor activity, and can instead involve the dissociation of the CS (motor) pathways and the spinothalamic (sensory) pathways. The end result of this dissociation may end with a contralesional motor pathway and an ipsilesional sensory pathway. Refer to Figure 1.1. for a diagram showing the dissociation of the SM pathways.

Asymmetric brain lesions can result in impaired development of UL motor skills (e.g. congenital hemiplegia/UCP). The evidence for rehabilitative approaches currently available to improve UL activity of infants at risk of UCP is limited. Early detection and early intervention are developmentally advantageous and will now be discussed.
Figure 1.1. Diagrammatic representation of the dissociation of sensorimotor pathways following an asymmetric brain lesion.

**Description.** After reorganisation following an asymmetric brain lesion, dissociation occurs between the sensory and motor pathways. The sensory pathway is reorganised in the ipsilesional hemisphere and the motor pathway is reorganised in the contralesional hemisphere.

**Key.** The dotted line indicates the reorganised sensory pathway; the solid line indicates the reorganised motor pathway; and PH indicates the paretic hand.

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1.1.4. A critical window for the early detection of Unilateral Cerebral Palsy

A very early screening method which involves MRI and/or functional assessment (e.g. Prechtl’s Assessment of General Movements; GMs) may help to identify infants with asymBL. Identifying lesions on neonatal MRI and having a functional means of predicting the likelihood of UCP would enable infants, potentially at risk and suitable for early intervention, to receive services. Magnetic resonance imaging and GMs are two methods which have been documented as being highly sensitive for predicting CP in infants and children.\(^7^2\) Magnetic resonance imaging (MRI) has been used to predict UCP in children born preterm and at term.\(^6^3\) When an MRI is supplemented by GMs, this method can be
used to predict UCP in very preterm infants, including those who have congenital brain lesions.\textsuperscript{72} Specifically, GMs at three months post-term age are highly associated with white matter abnormalities on MRI at term age.\textsuperscript{72} Assessment of GMs is a well validated and reliable method for predicting CP, and is more sensitive at predicting CP compared to other motor assessments used in infancy.\textsuperscript{72,73}

The first 12 to 24 months of life provide a critical period of neurodevelopment, in which there is growth and developing connectivity of the CS tracts (motor pathways) and spinothalamic tracts (sensory pathways). There is some evidence to suggest that for infants with brain lesions, important phases of sensorimotor reorganisation may have already occurred during their first year of life.\textsuperscript{67} After a brain lesion has occurred, development of the damaged cortex is compromised and its remaining contralateral CS pathways (which connect the damaged cortex to the impaired UL) stop developing.\textsuperscript{67} Eventually, the synaptic space that these pathways initially occupied is taken over by the more active ipsilateral pathways which connect the intact cortex to the impaired UL.\textsuperscript{69} Both sets of CS pathways compete for synaptic space, which results in the ipsilateral CS pathway outgrowing the contralateral CS pathway. The implications of this competitive process are impaired UL motor control and subsequently, impaired UL activity.\textsuperscript{67,74}

1.1.5. A critical window for early upper limb intervention

The first three to six months of life following an asymmetric brain lesion may offer a critical window of opportunity for very early intervention. Interventions provided at this time could be aimed to activate the damaged SM cortex.\textsuperscript{67} Activating the damaged SM cortex could enhance its competitive ability to develop alongside the intact SM cortex, and ameliorate the effects of the lesion on UL motor activity.\textsuperscript{67} One proposed method of activating the damaged cortex is through Action Observation Training.

Action Observation Training (AOT) is based on action observation, whereby new motor skills can be learned by observing motor actions. Action Observation Training is a rehabilitative approach that combines the observation of daily actions with physical training of the observed actions, to reinforce the activation of motor areas.\textsuperscript{75} An example of this is watching video sequences of goal-directed UL actions in daily life activities, followed by repetitive practice of the observed actions with the impaired UL.\textsuperscript{75,76} This process appears to be facilitated by the Mirror Neuron System (MNS). It has been proposed that the MNS codes for the execution of motor actions, which implies that: (i) there are pre-existing motor representations in the motor cortex of hand movements; and (ii) the ability to match the physical features of an object with appropriate hand
movements in order to grasp the object effectively reflects a bias to move. Recent evidence suggests that this mechanism is present from birth (e.g. thumb sucking and grasping of the umbilical cord in utero), and yet little is known about its role in motor development.

1.1.6. The Mirror Neuron System: location and function

The Mirror Neuron System (MNS) is comprised of mirror neurons; specialised neurons which fire when one observes another person performing an action and when one executes the action, facilitating understanding of the action and subsequent imitation of that action. Mirror neurons were initially discovered in the premotor area (F5) of macaque monkeys and have since been identified in the rostral area of the inferior parietal lobule (PF) and the ventral premotor cortex of monkeys. Direct evidence for the presence of the MNS in humans is lacking; to the author’s knowledge there have been no studies published which have recorded single neurons from the proposed MNS in humans. There is a growing body of neurophysiological and brain-imaging studies providing indirect evidence for the existence of the MNS in humans. Transcranial Magnetic Stimulation (TMS) studies have claimed that the MNS exists in humans.

It was proposed that the human equivalent of the monkey MNS is formed by the pars opercularis of the posterior inferior frontal gyrus (Brodmann area 44), the rostral part of the inferior parietal lobule and the lower part of the precentral gyrus. Two meta-analyses have since been conducted on brain-imaging studies that investigated imitation related to the MNS and/or action observation. One meta-analysis examined twenty functional magnetic resonance imaging (fMRI) studies on humans imitating hand and finger movements. The authors concluded that the superior parietal lobule, inferior parietal lobule and the dorsal part of the premotor cortex are involved in human imitation. The other meta-analysis examined 125 brain-imaging studies (including fMRI and TMS) reporting on human mirror regions and concluded that the brain regions of humans with mirror properties are: the inferior frontal gyrus, dorsal and ventral premotor cortices, as well as the inferior and superior parietal lobules. These areas are consistently activated during tasks that involve performing hand actions after observing them. The functional role of the MNS in both monkeys and humans has been proposed to underlie the processes of imitation and understanding the actions of others in relation to oneself.
1.1.7. The Mirror Neuron System, action observation and imitation

Primate studies have found that mirror neurons fire during active hand movements (e.g. grasping an object) and also when hand actions are being observed. The specific hand actions of grasping, holding, manipulating and placing objects always result in activation of mirror neurons.\textsuperscript{50,79} It would appear that for primates, the MNS facilitates the process of performing hand actions that have previously been observed.

Human studies using fMRI have found that brain regions believed to comprise the human MNS are activated when observing and performing hand actions (e.g. grasping an object).\textsuperscript{91,92,94} Stronger activation in some of these brain regions was found when the hand action was contextual, such as grasping a cup to drink, or grasping a cup to put it away.\textsuperscript{94} It would appear that for humans, the MNS enables one to recognise and perform hand actions that have been observed, and also facilitates an understanding of the intended action given the context of the action.\textsuperscript{94}

Demonstration of the MNS soon after birth may provide a new opportunity for an intervention for infants with congenital brain injury. Emerging evidence of action observation in human infants using electroencephalogram (EEG) and functional near-infrared spectroscopy (fNIRS) suggests that a visual-motor matching process involving action perception and execution (e.g. grasping an object) is detectable as early as six months of age.\textsuperscript{95,96} This emerging evidence of action observation in human infants, combined with evidence from the basic sciences in infant rhesus macaque monkeys\textsuperscript{90,97} and evidence from brain-imaging and imitation studies in human adults,\textsuperscript{91,92,94} suggests that the immature MNS can facilitate the imitative capabilities of infants for goal-directed hand actions. If infants are able to consistently demonstrate imitative skills (e.g. imitating hand actions), their capacity to imitate, combined with their ability to develop hand skills, may predict later motor development.

1.1.8. Cortical reorganisation following a brain lesion

Brain injuries that impact on the SM system can lead to different types of functional impairment, depending on the size and site of the brain lesion, and the type of cortical reorganisation that occurs.\textsuperscript{70,74,98} Ipsilesional reorganisation (i.e. reorganisation occurring in the damaged motor cortex with part of the undamaged cortex remaining) allows for the motor cortex to become reconnected to the spinal cord, and is usually what is seen in adults who have a brain lesion.\textsuperscript{68} Contralesional organisation (i.e. reorganisation occurring in the undamaged cortex and existing motor projections remaining intact, instead of becoming retracted within the first months of life) is an alternative type of
reorganisation that is possible if the lesion occurs early in development. Contralesional organisation allows the undamaged cortex to directly control both upper limbs, which results in limited UL motor activity. Emerging evidence in humans suggests that the pattern of SM reorganisation after early brain injury is determined during the first year of life, and possibly within the first few months. It has been suggested that the MNS may influence cortical reorganisation associated with UL impairment, and can potentially be a target for very early intervention. See Figure 1.2. for a diagram comparing ipsilesional and contralesional reorganisation.

Figure 1.2. Diagrammatic representation of ipsilesional versus contralesional reorganisation following an asymmetric brain lesion and impact on upper limb function.

Figure 1.2.A. Ipsilesional reorganisation following a small asymmetric brain lesion. Description. Reorganisation occurs in the damaged motor cortex, with part of the undamaged cortex remaining intact. Upper limb function can be preserved; and improved with upper limb rehabilitation. This would result in improved upper limb function compared to contralesional reorganisation.

Figure 1.2.B. Contralesional reorganisation following a large asymmetric brain lesion. Description. Reorganisation occurs in the undamaged motor cortex, with existing projections remaining intact. Upper limb function is controlled by the undamaged cortex. If the lesion occurs early in development, upper limb function may be enhanced by upper limb rehabilitation. If the lesion occurs late in development, upper limb control may not be as effective.

Key. P indicates paretic hand.

Adapted and reprinted from Brain, Vol. 125, M. Staudt et al., Two types of ipsilateral reorganization in congenital hemiparesis: A TMS and fMRI study, pp. 2222-2237 © 2002, with permission from Oxford University Press.
1.1.9. Proposed impact of action observation on cortical reorganisation

The process of observing an action (i.e. action observation) leads to activation of the MNS and stimulates the CS system (motor pathways) prior to imitating the action\textsuperscript{84,100-102}. When the motor cortex is damaged (e.g. congenital brain lesion), action observation and imitation may influence cortical reorganisation by directly restoring the damaged motor pathways or reinforcing other pathways that originally helped to perform motor actions, or both.\textsuperscript{103}

In animal and human adult studies, action observation appears to encourage activation of the MNS and enhance excitability of the SM cortex.\textsuperscript{75} These findings suggest that the effects of an asymmetric brain lesion in infants may be ameliorated by an UL rehabilitation program based on AOT. The aim of such a program would be to stimulate the competitive ability and growth of the damaged ipsilesional CS pathways (connecting the damaged cortex to the impaired UL), and subsequently modifying the contralesional reorganisation that can be seen after this type of injury. The proposed impact of AOT on brain reorganisation could influence UL motor development and function in infants with asymmetric brain lesions.

To date, AOT has been investigated in adults with chronic stroke\textsuperscript{75} and Parkinson’s disease.\textsuperscript{104} It has also recently been investigated in school-aged children (6-11 years) with CP\textsuperscript{105} and in school-aged children (5-15 years) with UCP.\textsuperscript{76,106} It has not been investigated in a population of infants with asymBI. The efficacy, benefits, feasibility of, and compliance with this novel rehabilitation for this at-risk population are therefore unknown. Ideally, such an intervention should begin soon after the brain injury has occurred, to encourage appropriate cortical reorganisation and development of UL actions. Voluntary reaching, however, is either immature or absent during the first weeks of life. It would be difficult, therefore, to observe voluntary activation of the motor cortex associated with purposeful hand movements during this early period. Activation of the motor cortex, specifically related to action observation, may instead be a way to target therapeutic intervention in this early period of development. For example, the intervention may involve: (i) infants observing adults reaching, grasping and releasing toys; and (ii) infants being presented with the same toys and being encouraged to reach, grasp and release the toys after observing the adults. Very early intervention should also be combined with standard rehabilitative approaches (e.g. occupational therapy and physiotherapy) as soon as infants can reach voluntarily, to reinforce the growth of cortical pathways and consolidate learning of UL motor skills. In adults with stroke, AOT has
been reported to increase cortical excitability of the SM cortex based on fMRI.\textsuperscript{75} It has also been reported to improve UL motor function; with small improvements identified in the treatment group only on the Frenchay Arm Test and the Wolf Motor Function Test.\textsuperscript{75} In school-aged children with CP, AOT has been reported to improve UL motor function on the Melbourne Assessment Scale; with significant improvements identified in the treatment group only.\textsuperscript{105} In school-aged children with UCP, AOT has been reported to improve the use of the impaired UL in bimanual activities on the Assisting Hand Assessment\textsuperscript{106} and preserve cortical activation in the ipsilesional motor cortex on fMRI.\textsuperscript{107} Based on the hypothesis that the same activation that has been demonstrated in adults with stroke and children with CP can be elicited in infants who are at high risk of UCP, AOT may enhance the excitability of the SM cortex, accelerate the maturation of the CS tract and the shaping of spinal motor circuits.

This section of Chapter 1 has provided a rationale for early detection of UCP and early UL intervention for infants who are at high risk of UCP by the end of their first year of life. Action Observation Training appears to be an intervention that has potential to influence the early development of UL motor skills in infants with asymBI. There are various other interventions with potential to improve other outcomes in infants with asymBI, such as prehensile skills, bilateral hand function, use of the impaired UL in bilateral tasks, and overall motor development, which will be addressed in the following section of this chapter. Aim 1 will be addressed by summarising paper 1, a book chapter that reports the current evidence for other UL interventions for infants with asymBI, at the time of the book’s publication in September 2013.

1.1.10. \textit{Paper 1: Very early upper limb interventions for infants with asymmetric brain lesions}

This paper comprises Chapter 13 in a book entitled ‘Cerebral Palsy in Infancy’ and was published in September 2013 (Appendix 9.1.). The bibliographic details are: Boyd RN, Perez M, Guzzetta A. \textit{Very early upper limb interventions for infants with asymmetric brain lesions.} (2013). Chapter 13 in R. Shepherd (Ed.), Cerebral Palsy in infancy. Oxford, UK: Elsevier ©, and is reproduced with permission from Elsevier. Key findings of this paper were:

- Brain MRI at term combined with a General Movements assessment (GMs) in the fidgety period (4 to 12 weeks corrected age, C.A.) are currently the most predictive methods for an early diagnosis of CP.
Neuromotor assessments such as the Bayley Scales of Infant and Toddler Development (BSID versions II and III) and the Test of Motor Performance (TIMP) used in the neonatal period have demonstrated moderate to strong validity to detect CP in preterm infants at 12 months C.A.

Asymmetry of fidgety GMs at 12 weeks C.A. can be used as a definitive clinical sign of UCP; while asymmetries in unimanual and bimanual reaching at 4 to 6 months C.A. can be a strong early indicator of UCP.

More research is required to determine efficacy, feasibility and safety of UL therapies for infants with asymmetric brain lesions, which have been shown to be effective and feasible for school-aged children with CP.

Optimal brain plasticity can be achieved when interventions include: intensive task-oriented repetition, incremental challenges with increasing difficulty, and the use of motivators or rewards; as demonstrated in school-aged children with CP.

Early interventions that show promise for infants with asymmetric brain lesions are: bilateral stimulation of hand function, modified Constraint Induced Movement Therapy (mCIMT), and Action Observation Training (AOT); although the efficacy and feasibility of these interventions for this young and at-risk population remain unclear.

Very early training of prehensile skills in infants at risk of or showing signs of UCP should be explored as a potential infant-friendly intervention, as it may enhance brain plasticity associated with skill development before learned non-use of the potentially impaired UL can develop.

To date, limited valid and reliable measures of early UL function (such as unimanual and bimanual reach and grasp behaviours) have been developed. Further valid and reliable measures of UL function for infants younger than six months C.A. are required to detect atypical UL development; predict delayed FM development; and examine the efficacy of early interventions. This section of Chapter 1 addressed Aim 1 by summarising paper 1, a book chapter published in September 2013 that reported the current evidence for UL interventions (including AOT) for infants with asymBI. The final section of Chapter 1 describes the outline and format of the thesis, as well as aims and hypotheses of the doctoral program.
1.2. Thesis outline

There is a paucity of available evidence to support the efficacy of UL motor interventions specifically for infants younger than three years of age with asymBI, who are at high risk of UCP by their first year of life. A systematic review (SR) was undertaken to examine the available evidence for non-surgical UL motor interventions based on SRs and randomised controlled trials (RCTs) for this young and at-risk population.

The most effective and established method to determine the efficacy of any intervention is to conduct a randomised controlled trial (RCT). Trials conducted in this rigorous manner, particularly when study populations include infants, can account for maturation of UL motor development by enabling comparison between experimental and control groups. This doctoral program was embedded within a larger study funded by the Australian Research Council (ARC), ‘The UP-BEAT Study’, which was comprised of two parallel RCTs. For this young and at-risk population however, a sham control design rather than a conventional control was necessary, primarily because it would not be ethically sound to deprive a high risk population of any intervention, particularly one that aims to improve long-term UL motor outcomes in infants. It was not appropriate to utilise a wait-list design in this intervention trial, as the developmental period of the infants would be different between the immediate start group and the wait-list group. The active ingredient of the intervention was demonstration by the infant’s caregiver of grasping a standard set of toys. The sham control involved the caregiver presenting the toys to the infant, without demonstrating the grasping action. The sham control was considered typical of toy exploration, whereby an infant spontaneously explores a toy (rather than observing how to play with a toy from a caregiver, which may result in imitation).

The use of valid and reliable measures is critical for examining and demonstrating change in response to interventions. There is, however, a paucity of available literature for measuring efficacy of UL motor interventions for infants younger than three years at risk of UCP, using valid and reliable UL motor function measures. There is also limited use of valid and reliable measures in available literature to: (i) accurately detect UCP; (ii) evaluate and quantify early abnormalities in UL motor development to predict UCP; and (iii) measure meaningful change following suitable UL motor interventions in infants with asymBI (who are younger than 12 months C.A.). To address the gap in the evidence base for a valid and reliable, quantitative measure of early UL development (e.g. asymmetries in early reach and grasp behaviours) in infants with asymBI, younger than 12 months C.A., this doctoral program sought to develop, test and report on a new
measure, the Grasp and Reach Assessment of Brisbane (GRAB). A validity study and a reproducibility study were undertaken on the GRAB, to evaluate its construct validity, internal consistency, intra- and inter-rater reliability and intra- and inter-rater agreement. It was anticipated that detailed information regarding the natural history/longitudinal development of UL motor activity, with a specific focus on the development of unimanual and bimanual reach and grasp behaviours in infants would be obtained from the GRAB. In addition, longitudinal reach to grasp development between infants with asymBI and healthy infants on the GRAB was hypothesised to predict later motor development on the BSID III by their first year of life. A longitudinal study was therefore undertaken in infants with asymBI and healthy infants, investigating the relationship between the GRAB and the BSID III. This doctoral program:

1. Systematically examines the evidence for early UL motor interventions on UL motor function in infants younger than three years with asymBI (including UCP);
2. Highlights the current gap in available evidence for UL motor function measures to detect and/or predict UCP and measure change in response to interventions in infants with asymBI;
3. Describes the development of a quantitative UL measure, the GRAB, for detecting and evaluating asymmetries in the early development of reach to grasp in both infants with asymBI and healthy infants;
4. Evaluates and reports construct validity and internal consistency of the GRAB;
5. Evaluates and reports intra- and inter-rater reproducibility of the GRAB;
6. Examines and describes longitudinal development of reach to grasp at 14, 16 and 18 weeks C.A. on the GRAB, in relation to prediction of delayed motor development at six and 12 months C.A. on the BSID III, in infants with asymBI compared to healthy infants.

1.3. Format of thesis

This thesis is presented as a series of five papers (published or submitted and currently under review) in international peer-reviewed journals. Chapter 1 addressed the rationale for the thesis and the state of current evidence for UL motor interventions for infants with asymBI, which summarised the first paper; a published book chapter entitled ‘Very early upper limb interventions for infants with asymmetric brain lesions’ (full paper is included as Appendix 9.1.). Chapter 2 presents the second paper; a systematic review entitled ‘Efficacy of upper limb interventions for infants (younger than three years) with asymmetric brain injury: A systematic review’. Chapter 3 addresses the study design and
Micah Perez - Thesis Chapter 1

methods of the doctoral program, which is embedded in a larger ARC-funded study, ‘The UP-BEAT Study’ (for which the published protocol paper is included as the fifth paper as Appendix 9.2.). Chapter 4 presents the third paper; a measurement paper entitled ‘Development, construct validity and internal consistency of the Grasp and Reach Assessment of Brisbane (GRAB)’. Chapter 5 presents the fourth paper; a measurement paper entitled ‘Intra- and inter-rater reproducibility of the measurements on the Grasp and Reach Assessment of Brisbane (GRAB). Chapter 6 presents the first draft of the final measurement paper on the GRAB, entitled ‘Assessment of reach to grasp to determine delayed motor development in infants with asymmetric brain injury’. Finally, Chapter 7 provides discussion of findings from this doctoral program along with: (i) strengths and limitations of this research; (ii) considerations for future research and implications for clinical practice; and (iii) conclusions.

1.4. **Aims and hypotheses**

This doctoral program evaluates the following aims and related hypotheses.

1.4.1. **Aims**

1. To systematically examine the efficacy of early UL motor interventions for infants younger than three years with asyBI (including UCP) in improving UL motor function, compared with usual care.

2. To develop the GRAB and then evaluate its construct validity and internal consistency.

3. To evaluate intra-rater and inter-rater reliability and agreement of the measurements on the GRAB.

4. To examine longitudinal development of reach and grasp behaviours at 14, 16 and 18 weeks C.A. on the GRAB, in relation to prediction of delayed motor development at six and 12 months C.A. on the BSID III in infants with asyBI compared to healthy infants.

1.4.2. **Hypotheses**

1. There will be limited evidence reporting the efficacy of early UL motor interventions for infants younger than three years with asyBI in improving UL motor function, compared with usual care.

2. The GRAB will demonstrate evidence for strong construct validity and internal consistency as a quantitative measure for: (i) detecting asymmetries between ULs in reach and grasp behaviours in infants with asyBI; and (ii) identifying
differences in reach and grasp behaviours between healthy infants and infants with asymBI at 18 weeks C.A.
3. The GRAB will demonstrate evidence for strong intra- and inter-rater reliability and high percentage intra- and inter-rater agreement of measurements within and between raters in healthy infants and infants with asymBI at 14, 16 and 18 weeks C.A.
4. Differences in the longitudinal development of reach to grasp behaviours between healthy infants and infants with asymBI at 14, 16 and 18 weeks C.A. on the GRAB, as well as differences between ULs in infants with asymBI at 14, 16 and 18 weeks C.A. on the GRAB will predict delayed motor development at six and 12 months C.A. on the BSID III in infants with asymBI compared to healthy infants.

Chapter 1 provided a rationale for undertaking this research in infants with early asymBI, drawing on available knowledge in neuroscience, basic sciences and UL motor development; the outline, format, aims and hypotheses of the thesis were also described. To address Aim 1, publication 1 was summarised, which was a book chapter that reported the current evidence for UL interventions for infants with asymBI, at the time of publication in September 2013 (see published chapter in Appendix 9.1.). The book chapter included the preliminary findings of the SR, which was updated to include current evidence up until February 2015. The updated SR also addresses Aim 1 and is presented as paper 2, which comprises Chapter 2.
Chapter 2: Literature Review

2.1. Introduction

This chapter addresses Aim 1 in the paper, ‘Efficacy of upper limb interventions for infants (younger than three years) with asymmetric brain injury: A systematic review’. This review systematically examines the efficacy of non-surgical UL motor interventions for infants (younger than three years) with asymBI in improving UL motor function, compared with usual care. It was predicted that there would be limited evidence reporting the efficacy of these interventions specifically for infants with asymBI.

2.2. Paper 2: Efficacy of upper limb interventions for infants (younger than three years) with asymmetric brain injury: A systematic review

This paper was resubmitted to Research in Developmental Disabilities on 12th October, 2015, and is currently under review.

Title
Efficacy of upper limb interventions for infants (younger than three years) with asymmetric brain injury: A systematic review

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Competing Interests
The authors declare they have no competing interests.
Authors’ Contributions
MP and RNB independently assessed abstracts and articles from the resulting search yield for eligibility for study inclusion. MP and LS independently underwent targeted reference scanning, citation tracking of key articles and hand-searching of papers written by key authors to minimise the chance of missing key studies. MP and JZ independently evaluated methodological quality of included systematic reviews using the PRISMA checklist and randomized controlled trials using a modified Downs and Black Scale. RNB and LS provided guidance in extracting and synthesising data from included randomized controlled trials. MP wrote the initial draft of the manuscript and all authors have read and approved the final manuscript.
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2.2.1. Abstract

This study systematically reviewed the efficacy of upper limb (UL) interventions to improve UL motor function in infants and children with or at risk of hemiplegia. Five databases were searched until February 2015. Inclusion criteria were: published systematic reviews (SRs) and randomised controlled trials (RCTs) that included infants (< 3 years) with or at risk of hemiplegia, who received non-operative UL interventions with UL motor function outcomes. Methodological quality was determined using PRISMA or a modified Downs and Black Scale.

Six SRs and 17 RCTs comprised 555 participants (of whom 50 < 3 years) with hemiplegia who received: signature constraint induced movement therapy (CIMT), modified CIMT (mCIMT), hybrid CIMT, forced use therapy (FUT), and occupational therapy (OT) supplemented with intramuscular UL Botulinum toxin A (BoNT-A) injections. Duration of all treatments ranged from 3 to 12 weeks. Total dosage ranged from 6 hours of OT (direct therapy) supplemented with a mean total dose 8U Botox®/kg/bodyweight to 255 hours of restraint wear and a unimanual intensive rehabilitation program. Total dosage of indirect therapy ranged from 12 hours of a ‘transfer package’ to 250 hours of a home exercise program. Analyses of effect size (ES) revealed: moderate to large effects for signature CIMT compared to usual care on unimanual UL function; small to large effects for mCIMT compared to usual care on unimanual outcomes; large effects for hybrid CIMT compared to usual care on unimanual and bimanual outcomes; large effects for hybrid CIMT compared to usual care on unimanual outcomes and small to moderate effects on bimanual outcomes; and small to moderate effects for OT supplemented with BoNT-A on unimanual outcomes compared to OT alone. There was limited data on feasibility, acceptability and safety with interventions for this group, particularly for at-risk infants.

There remains a paucity of evidence for the efficacy of non-operative UL interventions for infants with or at risk of hemiplegia. Only one RCT included participants who were all younger than three years. Signature CIMT and mCIMT appear more effective than usual care in improving unimanual and bimanual UL function; and contemporary approaches such as hybrid CIMT and OT with supplemented with BoNT-A appear more effective than usual care in improving unimanual and bimanual UL function. Further research is needed to determine efficacy for UL interventions during this critical period of development for infants at high risk of hemiplegia.
2.2.2. Introduction

Infants with asymmetric brain injury (asymBI) are at high risk of developing congenital hemiplegia by the end of their first year of life. Asymmetric brain lesions (e.g. intraventricular haemorrhages, periventricular leukomalacia, arterial strokes and venous infarctions) are common examples of asymBI, occurring in one to two of every 1000 newborns at birth. Congenital hemiplegia is the most common type of cerebral palsy (CP), with a prevalence of one in 1300 live births. These infants have impaired upper limb (UL) motor function, resulting in activity limitations and participation restrictions in daily life (e.g. feeding, play and self-care).

Recently published systematic reviews (SRs) of UL interventions, comprising school-aged children with CP (including congenital hemiplegia) have indicated that there is moderate to strong evidence for activity-based, goal-directed UL interventions such as signature constraint induced movement therapy (CIMT), modified CIMT, hybrid CIMT, forced use therapy (FUT) and occupational therapy (OT) supplemented with intramuscular UL botulinum toxin A (BoNT-A) injections to improve UL motor function.

With emerging research investigating early intervention for infants (younger than three years) at risk of hemiplegia, the efficacy of existing non-surgical UL interventions for this younger, at-risk population is unclear. A recently published SR has suggested that early enriched environments (including active motor training) are promising for enhancing recovery after a brain injury in infants at risk of CP. Early environmental enrichment (EE) can enhance UL intervention by providing opportunities for motor learning through different modalities such as active motor training, parental education and environmental adaptation. In contrast to traditional UL interventions, two important components of EE are involvement of the family and optimising the home environment.

Early intervention is considered important for improving UL motor function (e.g. reaching, grasping, manipulation, feeding and self-care) in at-risk infants during critical periods of development. Rehabilitation programs, however, do not generally commence until after six months of age, mostly due to delayed detection. Increasing use of General Movements in clinical practice will enable earlier detection of CP risk by 12 weeks corrected age, which will enable earlier commencement of intervention during the critical period of neuroplasticity. Better understanding of the potential and/or efficacy of
early interventions to enhance brain recovery and improve UL motor function is needed to inform health care providers and the families of at-risk infants.

To our knowledge, this SR is the first to investigate the efficacy of non-operative UL interventions (such as occupational therapy, physiotherapy, bimanual training, constraint induced movement therapy, forced use therapy and neurodevelopmental treatment) suitable for infants younger than three years of age with asymBI to improve UL motor function. This SR also aims to shed light on the feasibility and key ingredients of UL interventions for infants who are at risk of hemiplegia, according to the theoretical underpinnings of each intervention.

2.2.3. Methods

Search strategy

The following databases were comprehensively searched: Pubmed (1980-February 2015), CINAHL (1982-February 2015), Embase (1980-February 2015), Web of Science (1945-February 2015), Scopus (1980-February 2015) and The Cochrane Database of Systematic Reviews and Controlled Trials (1999-February 2015). The search strategy comprised key words (i.e. MeSH headings) where available, such as “infant” and “cerebral palsy” and “rehabilitation” and “upper extremity” (Appendix 2.1.).

Selection Criteria

Studies were included for review if they met the following criteria: (i) included infants (< 3 years) with asymBI or with a confirmed diagnosis of congenital hemiplegia; (ii) reported non-operative interventions (including occupational therapy, physiotherapy, bimanual training, constraint induced movement therapy, forced use therapy, neurodevelopmental treatment) aiming to improve UL motor function and/or reduce activity limitations; (iii) reported non-operative interventions with or without adjunctive therapy (including splinting, casting, intramuscular UL Botulinum toxin A and neuromuscular electrical stimulation); (iv) reported outcomes that included UL motor function (e.g. reaching, grasping, self-care, bimanual hand use); (v) were systematic reviews, randomised or quasi-randomised controlled trials; and (vi) were full text, published articles. Adjunctive therapy refers to an adjunct to therapy, which is not the primary therapy. For example, occupational therapy (OT) supplemented with intramuscular UL Botulinum toxin A (BoNT-A) is a type of intervention, whereby OT is the primary therapy, and BoNT-A is the adjunctive therapy. In this instance, the aim of this combined approach is to administer BoNT-A to reduce UL spasticity, in order to maximise potential benefits of goal-directed training with OT following BoNT-A.
Studies were excluded if they: (i) reported interventions which did not primarily focus on improving UL motor outcomes; (ii) reported surgical procedures (including UL surgery, selective dorsal rhizotomy and intrathecal baclofen); (iii) solely compared different dosages of intramuscular UL BoNT-A injections between groups; (iv) were duplicate studies that used the same study sample to report different outcomes; and (v) were not published in English (due to lack of translation services). A flowchart diagram of included and excluded studies is presented in Figure 2.1.

Eligibility for study inclusion was assessed independently by two authors (MP, RB). Titles and abstracts of the initial yield were screened by both authors, who reached consensus for articles that were potentially relevant and those that were not. Full texts were then retrieved and assessed for adherence to the full inclusion criteria. Targeted reference scanning, citation tracking of key articles and papers written by key authors were also performed by two authors (MP, LS) to minimise the chance of missing key studies. Only RCTs (including those identified from SRs) that met criteria were included in this SR, to enable comparison of UL motor development and maturation of FM skills between experimental and control groups. This comparison may not have been feasible with the inclusion of less rigorous studies, which were excluded from this review.

Data Extraction

Study design and participant demographics were extracted from included studies: including systematic reviews (SRs; Appendix 2.2.) and randomised controlled trials (RCTs; Table 2.1.). The content, dosage and method of delivery of interventions were extracted from included RCTs (Table 2.2.). Two authors (MP, JZ) independently evaluated the methodological quality of all included studies and discussed with a third author (RB) until 100% agreement was reached. The PRISMA checklist was used to evaluate SRs (Table 2.3.); and a modified Downs and Black Scale\textsuperscript{111} was used to evaluate RCTs (Table 2.4.). The Downs and Black Scale was chosen as it is a valid and reliable tool for evaluating the methodological quality of randomised studies and considers sample size and power; and its quality index has high test-retest reliability ($r=0.88$), good inter-rater reliability ($r=0.75$) and high criterion validity (0.90).\textsuperscript{111} Upper limb motor outcomes from included trials are reported in Table 2.5.

Data Synthesis

As previously reported in the SR of UL motor interventions for school-aged children with hemiplegia,\textsuperscript{13} interventions were categorised into five groups based on intervention type: (i) signature constraint induced movement therapy (CIMT), which
involved restraint wear with casting and shaping (training involving unimanual tasks and activities of daily living); (ii) modified CIMT (mCIMT), which involved alternative restraint wear to casting and unimanual training and/or a home program; (iii) hybrid CIMT, which involved a combined approach of CIMT and a ‘transfer package’ (home program involving bilateral training) or mCIMT and bimanual therapy; (iv) forced use therapy (FUT), which involved restraint wear with casting and without additional training; and (v) occupational therapy (OT) supplemented with intramuscular UL BoNT-A injections.

Where possible, comparisons between intervention and control groups for each UL outcome measure and for continuous measurement scales were determined using effect size (ES) calculations with 95% confidence intervals. Effect sizes were interpreted according to Cohen’s conventions, whereby 0.2 indicates a small ES; 0.5 indicates a moderate ES and 0.8 indicates a large ES.\textsuperscript{112}

\subsection*{2.2.4. Results}

\textit{Description of studies}

The search strategy yielded 664 articles, of which 472 were examined more closely by two independent reviewers (MP and RB; Figure 2.1.). Of these, six SRs and 17 RCTs met inclusion criteria; however, only one RCT included participants who were all younger than three years.\textsuperscript{5}

\textit{Study participants}

Seventeen RCTs were included, investigating 555 participants, of whom 50 (9\%) were identified as younger than three years of age. Ages of participants ranged from seven months to 14 years. The mean age of participants and ratio of males to females across all studies combined was unable to be reported for infants younger than three years of age, due to incomplete reporting in individual studies. All studies included diagnostic criteria of congenital hemiplegia.

All RCTs were included in this review despite the wide age range to provide a basis for examining the use of non-operative UL interventions for young infants and to demonstrate the intent of previous studies to include this younger age range. Such intent was thought to indicate perceived feasibility of interventions.

\textit{Methodological quality of studies}

The mean methodological quality rating for included SRs according to the PRISMA checklist was 19 out of a total possible score of 27 (range 12-24; Table 2.3.). The mean methodological quality rating for included RCTs according to the Downs and Black Scale was 18 out of a total possible score of 28 (range 14-24; Table 2.4.). Seven RCTs were
considered to be of fair quality (scored between 15-19); six were considered to be of good quality (scored between 20-24); and the remaining four RCTs were considered to be of poor quality (each scored 14).

**Intervention type**

Five intervention categories were identified (Table 2): (i) signature CIMT (2 publications of the same study\(^{113,114}\)); (ii) mCIMT (8 studies\(^{5,115,116-121}\)); (iii) hybrid CIMT (2 studies\(^{122,123}\)); (iv) FUT (2 studies\(^{124,125}\)); and (v) OT supplemented with intramuscular UL BoNT-A injections (3 studies\(^{126,127,128}\)).

**Method of delivery, duration and dosage of interventions**

Full details of method of delivery, duration and dosage of interventions according to each intervention category for included RCTs are presented in Table 2.2. The framework utilised to describe and compare interventions is closely aligned with the Frequency, Intensity, Time and Type (FITT) Principle\(^{129}\), which is a framework commonly used to describe key characteristics of exercise interventions.\(^{130,131}\) Interventions were delivered by trained therapists at a clinic\(^{113,114,124,125,127}\), often followed by a home program that was delivered by caregivers.\(^{115-119,121,122,126,128}\) The remaining interventions were delivered by caregivers and/or teachers in the community.\(^{115,120,123}\) Duration of interventions delivered by therapists across all studies ranged from three weeks of signature CIMT\(^{114}\) to 10 weeks of mCIMT.\(^{121}\) Thirteen studies provided adequate information regarding the total dosage of UL therapy, while the remaining four did not.\(^{5,124,125,127}\) Total dosage of restraint wear as a component of mCIMT ranged from 12 hours in a clinical setting\(^{118}\) to 280 hours at home.\(^{117}\) Occupational therapy was supplemented with a mean total dose of UL intramuscular UL BoNT-A injections ranging from 4.1U Botox®/kilogram/bodyweight\(^{127}\) to 8U Botox®/kilogram/bodyweight.\(^{128}\) Total dosage of direct therapy (i.e. provided by trained therapists in a clinical setting) ranged from six hours of OT supplemented with mean total dose 8U Botox®/kilogram/bodyweight\(^{128}\) to 255 hours of restraint wear and a unimanual intensive rehabilitation program.\(^{121}\) Total dosage of indirect therapy (i.e. provided by caregivers and/or teachers as part of a home program in the home and/or school environments) ranged from 12 hours of a ‘transfer package’\(^{123}\) to 250 hours of a home exercise program.\(^{119}\) Time of follow-up ranged from 3 weeks post-intervention, with no further follow up\(^{113}\) to 12 months follow-up.\(^{126}\)
Outcome measures for UL motor function

Outcome measures reported in this review included both unimanual and bimanual UL motor function components. Outcome measures for unimanual UL motor function with reported validity and reliability included: the Quality of Upper Extremity Skills Test (QUEST); the Box and Blocks Test (BBT); and the Erhardt Developmental Prehension Assessment (EDPA). The original version of the PMAL has inadequately reported validity and reliability; whereas both revisions of the PMAL (both called PMAL-R) have demonstrated fair construct validity and test-retest reliability. Overall the PMAL has limited psychometric data, with each version consisting of different items, rating scales and mode of administration. The Paretic Arm Use Test (PAUT), Pediatric Arm Function Test (PAFT) and Inventory of New Motor Activities and Programs Instrument (INMAP) were non-standardised outcome measures, used in single studies only. Outcome measures for bimanual UL motor function (including self-care) with established validity and reliability included: the Assisting Hand Assessment (AHA); the ABILHAND-Kids; the Peabody Developmental Motor Scales fine motor subscale (PDMS-FM); the Pediatric Evaluation of Disability Inventory self-care domain (PEDI); and the WeeFIM self-care domain (adapted for children from the adult version of the Functional Independence Measure).

Quantitative assessment

Outcomes of interest (interventions, population, number of included RCTs, inclusion of a meta-analysis and clinical inferences) for each SR are summarised in Appendix 2.2. Based on the findings of published SRs there is moderate to strong evidence for the efficacy of signature CIMT, mCIMT and OT supplemented with intramuscular UL BoNT-A injections to improve function of the impaired UL in children with hemiplegia. The critical dosage of these interventions, particularly for infants younger than three years, is unclear for improving UL motor outcomes. There is strong evidence for small effects of environmental enrichment (EE) to improve motor outcomes in infants and children up to seven years; however, there were methodological limitations across studies including inconsistent definitions of EE. There is inconclusive evidence for the efficacy of FUT to improve UL outcomes, due to the methodological limitations of available studies. Randomised controlled trials within SRs that met inclusion criteria were then extracted from each SR and analysed quantitatively.

A meta-analysis of pooled RCTs was not able to be performed as data on infants younger than three years could not be extracted. Effect sizes (ES) were calculated for
outcomes in 13 of the 17 included RCTs. Five of the 17 studies were not included in the ES analysis due to: one study reporting mean scores only without standard deviations\textsuperscript{124}; three studies reporting mean change scores only\textsuperscript{118,119,127}; and the remaining study based on a subsample of an earlier study.\textsuperscript{113}

*Primary outcomes for UL motor function*

Unimanual UL motor outcomes of included studies are summarized in Table 2.5. Moderate to large effects were identified for signature CIMT to improve the UL motor function of the impaired UL, compared to usual care (ES 0.76-1.66, PMAL\textsuperscript{114}). Mixed effects were identified for mCIMT on unimanual UL function, compared to usual care, ranging from: (i) no additional effects (ES -0.13, Besta Scale\textsuperscript{121}) to small effects on unimanual UL function (ES 0.49, QUEST\textsuperscript{120}); (ii) small effects (ES 0.32-0.38, PMAL-R\textsuperscript{116}) to large effects to improve unimanual function of the impaired UL (ES 1.02, PAUT\textsuperscript{117}). Large effects were identified for hybrid CIMT on unimanual UL function, compared to usual care, ranging from ES 0.98 (PAFT) to ES 3.80 to improve unimanual function of the impaired UL (PMAL\textsuperscript{123}). Mixed effects were identified for FUT on unimanual UL outcomes, compared to standard OT, ranging from no additional effects on fine motor skills of the impaired UL (ES 0.16, BBT), to small effects on the development of unimanual prehensile skills (ES 0.32, EDPA) on the EDPA.\textsuperscript{125} Mixed effects were also identified for OT supplemented with intramuscular UL BoNT-A injections to improve unimanual UL function, compared to standard OT, ranging from small effects (ES 0.42, QUEST\textsuperscript{126}) to moderate effects (ES 0.57, QUEST\textsuperscript{128}).

Bimanual UL motor outcomes of included studies are summarized in Table 2.5. Mixed effects were identified for mCIMT to improve bimanual coordination on the AHA, compared to standard OT or HABIT, ranging from small effects (ES 0.37\textsuperscript{116}) to large effects (ES 1.20\textsuperscript{120}). In contrast, negligible effects were found for mCIMT compared to NDT (ES -0.55\textsuperscript{115}). Mixed effects were identified for hybrid CIMT on bimanual UL outcomes, compared to usual care, ranging from small effects on bimanual coordination (ES 0.38, AHA\textsuperscript{122}) to moderate effects on bimanual self-care ability (ES 0.79, ABILHAND-Kids\textsuperscript{122}). Moderate effects were identified for FUT to improve self-care ability on the WeeFIM, compared to standard OT (ES 0.59\textsuperscript{125}). Mixed effects were identified for OT supplemented with intramuscular UL BoNT-A injections on bimanual outcomes, compared to standard OT alone, ranging from small effects on fine motor skills (ES 0.22, PDMS-FM\textsuperscript{126}) to moderate effects on functional self-care skills (ES 0.72, PEDI\textsuperscript{128}).
Compliance and participant retention

Compliance with interventions and participant retention for included RCTs are presented in Appendix 2.3. Compliance with interventions for each intervention category was 100%, except for mCIMT, which ranged from 70% (7/10 participants115) to 100%.116-118,120,121,125 Three mCIMT studies reported some inability to complete the prescribed intervention protocol.5,115,119 Participant retention at follow-up was the highest (100%) following signature CIMT113,114 and the lowest (58%) following FUT (7/12 participants124). Several studies reported incomplete follow-up, including three mCIMT studies5,115,119; and one of signature CIMT123 and FUT.124 It was not possible to separate data on compliance and retention in children who were younger than three years.

Adverse events associated with UL interventions

A summary of adverse events (AEs) associated with interventions of included RCTs is presented in Appendix 2.4. There were no serious AEs reported. Mild skin irritations were noted in almost half of the children in the signature CIMT study following casting114. There were no AEs reported following mCIMT, hybrid CIMT or FUT. Mild AEs following intramuscular UL BoNT-A injections were reported for a single child in two studies: (i) temporary soreness at the injection site118; and (ii) mild skin irritations.126 Moderate AEs following intramuscular UL BoNT-A injections were reported for 9 children: (i) seven with grip weakness118,127; (ii) two with finger weakness.126 In addition, vomiting following sedation was reported for a single child in one study.118 It was not possible to separate the reporting of AEs in children younger than three years.

2.2.5. Discussion

This systematic review identified a paucity of data on the efficacy of non-operative UL interventions for infants younger than three years of age with or at risk of hemiplegia. Based on included studies, evidence is emerging for the efficacy of signature CIMT, mCIMT, hybrid CIMT, FUT and OT supplemented with intramuscular UL BoNT-A injections to improve motor function of the impaired UL in infants with hemiplegia. The evidence for the efficacy of FUT remains inconclusive. Environmental enrichment is promising to support improvements in motor outcomes in infants and children (up to seven years) with or at risk of CP. This review was unable to draw conclusions for the critical dosage of these interventions, particularly for infants with asymmetric brain injury who were younger than three years; and methodological limitations were reported in all trials.
Only 12 out of the 17 included RCTs could be included in the ES analysis; and of these, only one study comprised participants who were all younger than three years. Only 9% (50/555) of participants across all RCTs were identified as younger than three years of age. As early detection of CP is becoming more accurate with a GMs assessment at three months in high risk infants\textsuperscript{110}, it is important that effective therapies are identified to maximise this early period of neuroplasticity. Several interventions such as mCIMT and hybrid CIMT show promise in terms of feasibility, with no adverse events being identified to date. These interventions, however, require further evaluation in adequately powered RCTs, using valid and reliable measures for this very young and at-risk population.

**Efficacy of UL interventions**

Based on outcome measures for unimanual and bimanual UL motor function (with reported validity and reliability), UL interventions designed to improve unimanual outcomes (such as use of the impaired UL in bimanual tasks) appear to demonstrate positive effects on unimanual outcomes, whereas interventions designed to improve bimanual outcomes (such as bimanual coordination) appear to demonstrate positive effects on bimanual outcomes. In addition, mCIMT appears to be the most effective intervention for improving both unimanual and bimanual UL motor function in this young age group, due to its key ingredients of motor learning, a combined approach of restraint wear during goal-directed unimanual training, and intensive practice in various environments (including the home environment). Hybrid CIMT appears to be the most effective intervention for improving bimanual UL motor function in this young age group, due to its combined approach of restraint wear followed by goal-directed unimanual and bimanual training. The efficacy of each intervention category is discussed below. The efficacy of each intervention category is discussed below.

**Efficacy of mCIMT (restraint wear with unimanual training) on unimanual outcomes**

Children who received mCIMT demonstrated small improvements in unimanual UL function on the QUEST, compared to children who received usual care.\textsuperscript{120,121} Only one study\textsuperscript{120} identified a clinically meaningful change of (> 13.8% total score) on the QUEST.\textsuperscript{135} Both of these studies utilised mCIMT based on motor learning and ecological theory, with intervention being delivered in a variety of environments (i.e. by therapists in a clinical setting as well as by parents at home and/or teachers in a school setting). The largest improvements in unimanual UL function were identified in the study that provided over 200 hours of parental-supervised restraint wear at home.\textsuperscript{117} The findings of this review indicate that the key elements of an effective mCIMT program to improve the use
of the impaired UL in bimanual activities in infants may be: (i) application of motor learning and ecological theory; and (ii) intensive, context-specific practice in familiar environments, such as the home and school environments.

**Efficacy of OT supplemented with BoNT-A on unimanual outcomes**

Children who received OT supplemented with intramuscular UL BoNT-A injections demonstrated small to moderate improvements (that were not clinically meaningful) in UL function on the QUEST, compared to children who received OT alone.\(^{126,128}\) Both studies utilised goal-directed training that was delivered by therapists in a clinical setting, followed by a home program.\(^{126,128}\) Improvements in UL function, however, were larger in one study,\(^ {128}\) which involved a single dose of intramuscular UL BoNT-A; compared to another study,\(^ {126}\) which involved three doses of intramuscular UL BoNT-A. The findings of this review indicate that: (i) multiple doses of intramuscular UL BoNT-A (which aim to reduce UL spasticity) do not appear to provide additional benefit to goal-directed unimanual training that is supplemented with a single dose of intramuscular UL BoNT-A; and (ii) goal-directed unimanual training followed by a home program may be a key element of an effective program of OT supplemented with intramuscular UL BoNT-A to improve unimanual capacity of the impaired UL in infants.

**Efficacy of mCIMT (restraint wear with unimanual training) on bimanual outcomes**

Children who received mCIMT demonstrated small to large improvements in bimanual coordination on the AHA, compared to children who received usual care.\(^ {5,116,120}\) Similar improvements in bimanual coordination were not demonstrated by another study\(^ {115}\), due to major differences between groups at baseline (AHA-units) and a small sample size (n=14; 7 treatment and 7 control). A clinically meaningful change (> 5 AHA-units) on the AHA post-treatment was identified in three out of four mCIMT studies.\(^ {5,115,120}\)

Each of these studies utilised mCIMT based on motor learning and ecological theory, with intervention being delivered in a variety of environments (i.e. by therapists in a clinical setting as well as by parents at home and/or teachers in a school setting). The largest improvements in bimanual coordination were identified in two studies; one providing a large dosage of clinician-supervised unimanual training, divided into 48 hours of individual and group training in a preschool setting\(^ {120}\), and the other involving a large dosage of an ‘ecoCIMT’ home program delivered by parents at home and teachers in a preschool setting.\(^ {5}\) The findings of this review indicate that the key elements of an effective mCIMT program to improve bimanual coordination in infants may be: (i) application of motor learning and ecological theory; (ii) intensive, context-specific practice.
in familiar environments, such as the home and school environments; and (iii) intensive practice in both individual and group settings.

**Efficacy of hybrid CIMT (restraint wear followed by unimanual and bimanual training) on bimanual outcomes**

In one study of hybrid CIMT\(^{122}\), children who received hybrid CIMT demonstrated a small yet clinically meaningful change in bimanual coordination on the AHA, as well as moderate improvements in self-care skills on the ABILHAND-Kids, compared to children who received usual care. It is unclear, however, what constitutes a clinically meaningful change on the ABILHAND-Kids.\(^{136}\) The intervention provided in the study\(^{122}\) utilised hybrid CIMT based on motor learning theory with goal-directed unimanual and bimanual training. The findings of this review indicate that, similarly to mCIMT, the key elements of an effective hybrid CIMT program to improve the use of the impaired UL in bimanual activities in infants may be: (i) application of motor learning theory with goal-directed training; (ii) context-specific practice within the home environment; and (iii) a combined approach involving goal-directed unimanual and bimanual training and practice in both individual and group settings.

**Efficacy of FUT (restraint wear without unimanual training) on bimanual outcomes**

In one small FUT study of poor quality\(^{125}\), children who received FUT demonstrated moderate improvements in self-care skills on the WeeFIM, compared to children who received OT alone. It is unclear, however, what constitutes a clinically meaningful change on the WeeFIM for this young age group.\(^{137}\) It must be noted that the description of FUT provided in this study appears to be more aligned to mCIMT, as the treatment group also received bimanual training (i.e. stretching exercises and OT). The findings of this review indicate that restraint wear may be beneficial for infants in addition to bimanual training, to improve bimanual self-care skills.

**Efficacy of OT supplemented with BoNT-A on bimanual outcomes**

Children who received OT supplemented with intramuscular UL BoNT-A injections demonstrated small improvements in FM skills on the PDMS-FM; and small to moderate improvements in self-care skills on the PEDI compared to children who received OT alone.\(^{126,128}\) It is unclear, however, what constitutes a clinically meaningful change on the PDMS-FM\(^{138,139}\) and the PEDI.\(^{140}\) Both studies utilised goal-directed training that was delivered by therapists in a clinical setting, followed by a home program.\(^{126,128}\) Improvements in UL function, however, were larger in one study\(^{128}\), which involved a single dose of intramuscular UL BoNT-A; compared to another study\(^{126}\), which involved
three doses of intramuscular UL BoNT-A. The findings of this review indicate that: (i) multiple doses of intramuscular UL BoNT-A (which aim to reduce UL spasticity) do not appear to provide additional benefit to goal-directed training that is supplemented with a single dose of intramuscular UL BoNT-A; and (ii) goal-directed training followed by a home program may be a key element of an effective program of OT supplemented with intramuscular UL BoNT-A to improve bimanual FM skills in infants.

**Compliance and participant retention**

Overall compliance with interventions was high, with only minor difficulties tolerating constraint in the form of casting\(^{124}\) and a glove or mitt in mCIMT.\(^{5,116}\) It was unclear, however, in two studies\(^{5,124}\) if these difficulties were encountered during therapy sessions with trained therapists or during the home program. Another study\(^{116}\) investigated the feasibility of mCIMT for children between 19 months and 7 years of age, and identified that 75% of parents reported difficulties with implementing mCIMT at home. Findings of the present review identified that compliance with constraint (signature CIMT, mCIMT, hybrid CIMT and FUT) overall was high, which suggests that families undertaking these interventions did not appear to have more difficulty accepting constraint as a component of an UL therapy program compared to usual care. Overall participant retention at follow-up was moderate (58%\(^{124}\)) to high (100%, e.g.\(^{121}\)). Loss to follow-up was most often attributed to child health problems, difficulty tolerating treatment, family situation and missed appointments.\(^{5,115,119,123,124,141}\) These reasons for loss to follow-up are similar to other trials that have investigated the efficacy of CIMT, mCIMT, intramuscular UL BoNT-A injections alone or as a supplement to OT in school-aged children with CP (e.g.\(^{142,143-146}\)).

**Adverse events associated with interventions**

There were no serious adverse events (AEs) reported in included RCTs; only mild or moderate AEs were reported for 16 out of 555 participants (3%). Classification of AEs did not employ the Common Terminology Criteria for Adverse Events\(^{147}\), which introduced ambiguity when making comparisons across studies and determining their relative suitability. The number of participants with reported AEs whom were younger than three years is unclear, due to incomplete reporting. As such, the suitability of interventions such as mCIMT, hybrid CIMT and OT supplemented with intramuscular UL BoNT-A injections for infants is unclear. It should also be noted that, as yet, intramuscular BoNT-A is not licensed for use in children under two years of age.
Future directions

It is generally accepted that early intervention for infants at risk for developing hemiplegia is beneficial, yet in reality, this does not usually commence until six months of age\(^6\), due to delayed detection and/or confirmed diagnosis of congenital hemiplegia. The accuracy of early detection is challenging, with the rate of CP in population-based cohorts of preterm-born infants being only 10%.\(^{148}\) In addition, there is limited use of accurate tools such as the Hammersmith Infant Neurologic Examination to detect CP in term-born, at-risk infants; approximately 50% of whom will later be diagnosed with CP.\(^{149}\) Currently, the best available detection of CP is with GMs at fidgety age (12 weeks post-term age) combined with MRI at term-equivalent age in high risk infants.\(^{150}\)

The findings of this review indicate that mCIMT, hybrid CIMT, FUT and OT supplemented with BoNT-A are more effective than usual care in improving bimanual UL motor function (on the AHA, ABILHAND-Kids, WeeFIM, PDMS-FM and PEDI). The evidence for interventions supporting improved unimanual function in the impaired UL for infants with or at risk of CP is less promising. This may be due to: (i) limitations in the interventions; (ii) limitations in accurately measuring unimanual function, as most available measures (both standardised and non-standardised) focus on specific components of function (e.g. quality of movement, amount and quality of use); and (iii) limited sensitivity of available measures of unimanual function (e.g. inadequate data on test-retest reliability). New versions of standardised measures (including the Melbourne Assessment of Unilateral Upper Limb function; MUUL), namely the Modified Melbourne Assessment (MMA, 2 to 4 years\(^{14,151}\)) with Rasch analysis into domains of grasping may have better sensitivity to detect changes due to intervention.

Further adequately powered RCTs commenced earlier using recently validated tools for the younger age range, such as the mini-Assisting Hand Assessment (mini-AHA\(^{12}\)) and the Hand Assessment of Infants (HAI\(^9\)) are urgently needed. Recent study protocols of baby-CIMT\(^9\) and baby Action Observation Training\(^{58}\) offer potential for intervention for infants with asymBI who are younger than 12 months of age.

The critical timing of available UL motor interventions for infants with asymBI remains unclear, as does the mode of delivery. Reported dosages and modes of existing interventions which have produced functional improvements in UL motor function remain highly variable. There is limited understanding of the optimal total dosage of direct therapy and/or the additional dose of indirect therapy. The wide variation in dosage of restraint wear in mCIMT (30 to 255 hours) and in hybrid CIMT (54 to 78 hours) suggests
that the type of therapy used for the impaired UL accompanying restraint of the unimpaired UL may be the active ingredient. The variations in mean total dose of intramuscular BoNT-A varying from 4.1U to 8U of Botox®/kg/bodyweight provide no clear direction for the additional benefits of higher doses. As such, the critical dosages and modes of these interventions for this very young population are unclear. It is likely that small episodes of therapy, applied repeatedly, may be needed at critical periods of reach to grasp development and at periods of early bimanual hand use.9

Findings from this review, which have been synthesised from RCTs that included infants with congenital hemiplegia, suggest that for this very young and at-risk population, mCIMT, hybrid CIMT, FUT and OT supplemented with intramuscular UL BoNT-A may be more effective than usual care in improving unimanual and/or bimanual UL motor function when these interventions are based on motor learning theory, involve goal-directed training, and are delivered in a variety of environments (including the home environment). Furthermore, mCIMT may be the most effective intervention for improving both unimanual and bimanual UL motor function in this young age group, due to its key ingredients of motor learning, a combined approach of restraint wear during goal-directed unimanual training, and intensive practice in various environments (including the home environment). Hybrid CIMT may be the most effective intervention for improving bimanual UL motor function in this young age group, due to its combined approach of restraint wear followed by goal-directed unimanual and bimanual training. Goal-directed training followed by an OT home program may be more beneficial than the additional use of BoNT-A to improve the use of the impaired UL in bimanual activities.13

In consideration of additional treatments such as intramuscular UL BoNT-A, there is no efficacy reported for infants younger than three years of age. The long-term effects of atrophy on the muscles injected once or with repeated injections of BoNT-A are unknown, and must be considered if early use of BoNT-A is to be tested in future RCTs. The effect of constraint in various forms on brain reorganisation (i.e. greater lateralisation of corticospinal pathways), though considered to be safe in a young animal model,152,153 has not been tested in infants with asymBI.

Interventions that focus on early motor training based on the principles of motor learning, prior to developmental disuse, could provide an alternative approach. Infant-friendly interventions, whereby the child is actively learning through playful and incrementally challenging activities within a naturalistic environment, offer the best opportunities for motor learning. There is considerable evidence for such interventions
based on animal models and basic science (e.g.\textsuperscript{154,155,156}). One recently published SR has appraised the efficacy of early environmental enrichment on the motor skills of infants at risk of or diagnosed with CP and identified small effects on motor outcomes.\textsuperscript{6} It is imperative that future research involves infants with asymBI and documents new interventions carefully, including: (i) evaluation of the efficacy of UL interventions aiming to improve unimanual and bimanual UL motor outcomes; (ii) consideration of potential effects based on theoretical underpinnings of the intervention, dosage, environment and method of delivery; and (iii) reporting of compliance, retention and adverse events with interventions. An individual patient data analysis for this very young and at-risk population is the next step to shed light on infant and intervention factors that may result in clinically meaningful outcomes.\textsuperscript{13}

\textit{Limitations}

There was potential for bias in this systematic review. Only studies with a strong study design (i.e. SRs and RCTs), published in English and that had full-text available, were included in this review. Some RCTs included in this review comprised small sample sizes and were of poor methodological quality, which resulted in difficulties interpreting the data. Only seven out of 17 RCTs reported a sample size power calculation and comprised an adequately powered sample size to detect a clinically meaningful change. Only one study population solely comprised infants younger than three years, and it was not possible to ascertain the number younger than three years for all of the studies. As a result, a meta-analysis of pooled studies was not able to be performed. Many of the included studies involved small sample sizes; there was considerable variability in the duration, dosages and method of delivery of interventions; and there were inconsistencies across studies in the reporting of outcomes and use of measures with inadequately reported validity and reliability. Reporting of compliance and retention of younger participants with interventions was incomplete. In light of these methodological limitations, the results of the ES analyses should be interpreted with caution; clinical implications of these interventions cannot be generalized to a population younger than three years; and the compliance and retention of participants in this very young and at-risk population remain unclear.

\textit{2.2.6. Conclusions}

Current evidence of non-operative UL interventions, which includes infants younger than three years with congenital hemiplegia, suggests that: signature CIMT and mCIMT are more effective than usual care in improving unimanual and bimanual UL
function; and contemporary approaches such as hybrid CIMT and OT supplemented with intramuscular UL BoNT-A injections are more effective than usual care in improving unimanual and bimanual UL function. These interventions appear to demonstrate positive effects on unimanual and bimanual UL motor function when they are based on motor learning theory, involve goal-directed training and are delivered in a variety of environments, including the home environment. It is recommended that further high-quality RCTs are conducted to investigate the efficacy and feasibility of UL interventions to improve unimanual and bimanual UL motor outcomes for infants at risk of CP.

**Figure 2.1.** Included and excluded studies.
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Diagnosis</th>
<th>Age</th>
<th>Treatment</th>
<th>(n)</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deluca 2006</td>
<td>RCT crossover</td>
<td>Congenital Hemiplegia</td>
<td>7-96 mths (9/18 &lt; 3 yrs)</td>
<td>CIMT (restraint and shaping)</td>
<td>9 (14-96 mths) (4/9 &lt; 3 yrs)</td>
<td>Control period (prior to CIMT)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>(9/18 &lt; 3 yrs)</td>
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<tr>
<td>Taub 2004</td>
<td>RCT</td>
<td>Congenital Hemiplegia</td>
<td>7-96 mths (9/18 &lt; 3 yrs)</td>
<td>CIMT (restraint and shaping)</td>
<td>9 (7-85 mths) (5/9 &lt; 3 yrs)</td>
<td>‘Usual care’ (OT or PT)</td>
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<td></td>
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<td></td>
<td>(5/9 &lt; 3 yrs)</td>
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<tr>
<td><strong>Modified constraint induced movement therapy (mCIMT)</strong></td>
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<tr>
<td>Gelkop 2014</td>
<td>RCT crossover</td>
<td>Congenital Hemiplegia</td>
<td>1.5-7 yrs (?/12 &lt; 3 yrs)</td>
<td>mCIMT (restraint and unimanual tasks)</td>
<td>6 (1.5-7 yrs) (7/6 &lt; 3 yrs)</td>
<td>HABIT</td>
</tr>
<tr>
<td>Hoare 2013</td>
<td>RCT</td>
<td>Congenital Hemiplegia</td>
<td>18 mths-6 yrs (?/34 &lt; 3 yrs)</td>
<td>mCIMT (restraint and unimanual training and HP) and BoNT-A</td>
<td>17 (?/17 &lt; 3 yrs)</td>
<td>BOT and BoNT-A</td>
</tr>
<tr>
<td>Xu 2012</td>
<td>RCT</td>
<td>Congenital Hemiplegia</td>
<td>2-14 yrs (?/68 &lt; 3 yrs)</td>
<td>(1) mCIMT (restraint and HP) and ES</td>
<td>(1) 23 (?/23 &lt; 3 yrs)</td>
<td>OT</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>(2) mCIMT (restraint and HP) and ES</td>
<td>(2) 22 (?/22 &lt; 3 yrs)</td>
<td></td>
</tr>
<tr>
<td>Al-Oraibi 2011</td>
<td>RCT</td>
<td>Congenital Hemiplegia</td>
<td>22-105 mths (3/14 &lt; 3 yrs)</td>
<td>mCIMT (restraint and unimanual training)</td>
<td>7 (2/7 &lt; 3 yrs)</td>
<td>NDT</td>
</tr>
<tr>
<td>Eliasson 2011</td>
<td>RCT crossover</td>
<td>Congenital Hemiplegia</td>
<td>20-39 mths (?/25 &lt; 3 yrs)</td>
<td>eco-CIMT (restraint and unimanual training)</td>
<td>12 (?/12 &lt; 3 yrs)</td>
<td>Care as usual (prior to eco-CIMT)</td>
</tr>
<tr>
<td>Fedrizzi 2013</td>
<td>RCT (cluster randomised)</td>
<td>Congenital Hemiplegia</td>
<td>2-8 yrs (32/105 &lt; 3 yrs)</td>
<td>(1) mCIMT (restraint and unimanual intensive rehabilitation program)</td>
<td>(1) 39 (10/39 &lt; 3 yrs)</td>
<td>‘Traditional rehabilitation program’ (PT for infants; OT for preschool and school-aged children)</td>
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<td></td>
<td>(2) Bimanual intensive rehabilitation program mCIMT (restraint and HP)</td>
<td>(2) 33 (13/33 &lt; 3 yrs)</td>
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<tr>
<td>Wallen 2011</td>
<td>RCT</td>
<td>Congenital Hemiplegia</td>
<td>19 mths -7 yrs (?/50 &lt; 3 yrs)</td>
<td>mCIMT (restraint and HP)</td>
<td>25 (?/25 &lt; 3 yrs)</td>
<td>OT</td>
</tr>
<tr>
<td>Smania 2009</td>
<td>RCT crossover</td>
<td>Congenital Hemiplegia</td>
<td>1-10 yrs (?/60 &lt; 3 yrs)</td>
<td>mCIMT (restraint and unimanual therapy) and PT</td>
<td>5 (?/5 &lt; 3 yrs)</td>
<td>PT</td>
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<tr>
<td><strong>Hybrid CIMT</strong></td>
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<tr>
<td>Taub 2011</td>
<td>RCT crossover</td>
<td>Congenital Hemiplegia</td>
<td>2-6 yrs (?/20 &lt; 3 yrs)</td>
<td>CIMT (restraint and shaping in play and ADLs) and ‘transfer package’/HP</td>
<td>10 (?/10 &lt; 3 yrs)</td>
<td>‘Usual care’ (OT or PT)</td>
</tr>
<tr>
<td>Aarts 2010</td>
<td>RCT</td>
<td>Congenital Hemiplegia</td>
<td>2.5-8 yrs (?/50 &lt; 3 yrs)</td>
<td>mCIMT-BIT (restraint and shaping and repetitive task practice, followed by bimanual task-specific training without restraint) and HP</td>
<td>28 (?/28 &lt; 3 yrs)</td>
<td>‘Regular rehabilitation program’ (OT and/or PT)</td>
</tr>
</tbody>
</table>

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## Table 2.1. (continued)

### Study design and participant demographics of included randomised controlled trials.

<table>
<thead>
<tr>
<th>Study Title</th>
<th>Design</th>
<th>Condition</th>
<th>Age Group</th>
<th>Intervention</th>
<th>Follow-Up</th>
<th>Comparator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sung 2005</td>
<td>RCT</td>
<td>FUT</td>
<td>&lt; 8 yrs</td>
<td>FUT with short-arm plaster cast</td>
<td>18 (?/12 &lt; 3 yrs)</td>
<td>OT</td>
</tr>
<tr>
<td>Willis 2002</td>
<td>RCT crossover</td>
<td>Congenital Hemiplegia</td>
<td>1-8 yrs (?/25 &lt; 3 yrs)</td>
<td>FUT with long-arm plaster cast</td>
<td>12 (?/12 &lt; 3 yrs)</td>
<td>Control period (prior to FUT)</td>
</tr>
<tr>
<td>Olesch 2010</td>
<td>RCT</td>
<td>Occupational therapy (OT) supplemented with BoNT-A</td>
<td>1-5 yrs (?/22 &lt; 3 yrs)</td>
<td>OT and BoNT-A</td>
<td>11 (?/11 &lt; 3 yrs)</td>
<td>OT</td>
</tr>
<tr>
<td>Lowe 2006</td>
<td>RCT</td>
<td>Occupational therapy (OT) supplemented with BoNT-A</td>
<td>2-8 yrs (?/42 &lt; 3 yrs)</td>
<td>OT and BoNT-A</td>
<td>21 (?/21 &lt; 3 yrs)</td>
<td>OT</td>
</tr>
<tr>
<td>Fehlings 2000</td>
<td>RCT</td>
<td>Occupational therapy (OT) supplemented with BoNT-A</td>
<td>2-10 yrs (?/29 &lt; 3 yrs)</td>
<td>OT and BoNT-A</td>
<td>14 (?/14 &lt; 3 yrs)</td>
<td>OT</td>
</tr>
</tbody>
</table>

**Key:** RCT indicates randomised controlled trial; CIMT, constraint induced movement therapy; mCIMT, modified constraint induced movement therapy; eco-CIMT, ecological approach of constraint induced movement therapy; mCIMT-BiT, modified constraint induced movement therapy combined with bimanual task-specific training; HABIT, hand-arm bimanual intensive therapy; ES, electrical stimulation; rehabilitation program; BoNT-A, intramuscular upper limb injections of botulinum toxin A; FUT, forced-use therapy; OT, occupational therapy; BOT, bimanual occupational therapy; HP, home program; mths, months; yrs, years; ?, unknown number.
Table 2.2. Content of intervention, method of delivery and dosage of interventions in included randomised controlled trials.

<table>
<thead>
<tr>
<th>Study</th>
<th>Content of Intervention Program</th>
<th>Duration of Intervention</th>
<th>Frequency and Dosage of Intervention Program</th>
<th>Delivery Method of Intervention</th>
<th>Content of Control Program</th>
<th>Duration of Control</th>
<th>Frequency and Dosage of Control Program</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Signature constraint induced movement therapy (CIMT)</strong></td>
<td></td>
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<tr>
<td>Deluca 2006</td>
<td>CIMT (restraint with bivalved lightweight fibreglass cast and shaping in unimanual tasks and ADLs)</td>
<td>3 wks</td>
<td>CIMT: restraint wear and shaping, 6hrs/day [42hrs/wk]</td>
<td>Total direct Rx (CIMT): 126hrs</td>
<td>Clinician-supervised</td>
<td>Control period prior to CIMT</td>
<td>3 wks</td>
</tr>
<tr>
<td>Taub 2004</td>
<td>CIMT (restraint with univalved lightweight fibreglass cast and shaping in unimanual tasks and ADLs)</td>
<td>3 wks</td>
<td>CIMT: restraint wear and shaping, 6hrs/day [42hrs/wk]</td>
<td>Total direct Rx (CIMT): 126hrs</td>
<td>Clinician-supervised</td>
<td>’Usual care’ (OT or PT)</td>
<td>3 wks</td>
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<tr>
<td><strong>Modified constraint induced movement therapy (mCIMT)</strong></td>
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<tr>
<td>Gelkop 2014</td>
<td>mCIMT (restraint with custom-made glove and progression of unimanual tasks)</td>
<td>8 wks</td>
<td>mCIMT: 2hrs/day for 6 days/wk [12 hrs/wk]; mCIMT(i): 1 hr/day [6 hrs/wk]; mCIMT(g): 1 hr/day [6 hrs/wk]</td>
<td>Total mCIMT (i): 48 hrs</td>
<td>Clinician-supervised within a kindergarten or preschool setting</td>
<td>HABIT</td>
<td>8 wks</td>
</tr>
<tr>
<td>Hoare 2013</td>
<td>mCIMT (restraint with neoprene glove and unimanual training and HP) and BoNT-A</td>
<td>12 wks: Single dose of BoNT-A, 8 wks</td>
<td>mCIMT: restraint wear, 0.75-1hr/day for 2 days/wk [1.5-2hrs/wk] with unimanual training, 0.75-1hr/day for 2 days/wk [1.5-2hrs/wk] HP: 3hrs/day for 7 days/wk [21hrs/wk]</td>
<td>Total direct Rx (mCIMT): 12-16hrs restraint &amp; 12-16hrs unimanual training</td>
<td>Clinician-supervised and HP, parents provided training at home</td>
<td>BOT and HP</td>
<td>12 wks: Single dose of BoNT-A, 8 wks</td>
</tr>
<tr>
<td>Xu 2012</td>
<td>(1) mCIMT (restraint with thermoplastic splint and HP(A+B)) (2) mCIMT (restraint with thermoplastic splint and ES and HP(A+B))</td>
<td>26 wks: 2 wks mCIMT with/without ES and HP(A): 24 wks HP(B)</td>
<td>mCIMT: restraint wear, 3hrs/day for 5 days/wk [15hrs/wk] with ES, 0.33hrs for 5 days/wk [1.7hrs/wk] HP(A): 1hr/day for 5 days/wk [5hrs/wk] HP(B): 2hrs/day for 5 days/wk [10hrs/wk]</td>
<td>Total direct Rx (restraint): 30hrs</td>
<td>Clinician-supervised and HP</td>
<td>OT</td>
<td>2 wks</td>
</tr>
<tr>
<td>Study</td>
<td>Intervention Details</td>
<td></td>
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<tr>
<td>Al-Oraibi 2011</td>
<td>mCIMT (restraint with custom-made glove and unimanual training) 8 wks mCIMT: restraint wear, 2hrs/day for 6 days/wk [12hrs/wk] with unimanual training, 1hr/wk [8hrs/wk] Total direct Rx (mCIMT): 160hrs Total indirect Rx (HP): 96hrs eco-CIMT: restraint wear with unimanual training, 2hrs/day [10hrs/wk] Total indirect Rx (eco-CIMT): 8hrs</td>
<td>Clinician-supervised and HP NDT 8 wks 1-2 hrs/wk Total direct Rx (NDT): 8-16 hrs</td>
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</tr>
<tr>
<td>Eliasson 2011</td>
<td>eco-CIMT (restraint with fabric glove with built-in stiff plastic volar splint and unimanual training) 8 wks eco-CIMT: restraint wear with unimanual training, 2hrs/day [10hrs/wk] Total indirect Rx (eco-CIMT): 8hrs</td>
<td>Clinician-supervised 1x/wk, training by parents at home or teachers at school Care as usual prior to eco-CIMT 8 wks No treatment provided to the control group</td>
<td></td>
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</tr>
<tr>
<td>Fedrizzi 2013</td>
<td>(1) mCIMT (restraint with fabric glove with built-in volar stiff plastic splint and unimanual intensive rehabilitation program at a rehabilitation centre and as HP) (2) Bimanual intensive rehabilitation program at a rehabilitation centre and as HP 10 wks mCIMT: restraint wear, 3hrs/day for 7 days/wk [21hrs/wk] with unimanual intensive rehabilitation program (rehabilitation centre and home), 3hrs/day for 3 days/wk [9hrs/wk], 1.5hrs/day with clinicians at the rehabilitation centre, and 1.5hrs/day with parents at home [4.5hrs/wk with clinicians; 4.5hrs/wk with parents]; and with intensive unimanual training (as HP), 3hrs/day for 4 days/wk at home [12hrs/wk] Bimanual intensive rehabilitation program (rehabilitation centre and home): 3hrs/day for 3 days/wk [9hrs/wk], 1.5hrs/day with clinicians and 1.5hrs/day with parents [4.5hrs/wk with clinicians; 4.5hrs/wk with parents]; and as HP, 3hrs/day for 4 days/wk at home [12hrs/wk] Total indirect Rx (mCIMT with clinicians): 255hrs Total indirect Rx (parents/HP): 57hrs of unimanual or bimanual intensive rehabilitation program 'Traditional rehabilitation program' (PT for infants; OT for preschool and school-aged children) 10 wks 1hr/day for 2 days/wk [2hrs/wk] Total direct Rx (OT/PT): 20hrs</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wallen 2011</td>
<td>mCIMT (restraint with fabric mitt with a solid thermoplastic volar insert and HP) 8 wks mCIMT: restraint wear, 2hrs/day [14hrs/wk] with HP, 0.33hr/day [2.3hrs/wk] Total direct Rx (mCIMT): 112hrs Total indirect Rx (HP): 18.4hrs</td>
<td>Clinician-supervised and HP OT 8 wks OT: 1hr/wk HP: varied, recommended time 0.33hr/day Total direct Rx (OT): 8hrs Total indirect Rx (HP): 18.5hrs</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>
### Table 2.2. (continued)
**Content of intervention, method of delivery and dosage of interventions in included randomised controlled trials.**

<table>
<thead>
<tr>
<th>Study Year</th>
<th>Intervention Details</th>
<th>Duration</th>
<th>Intervention Dosage</th>
<th>Method of Delivery</th>
<th>Direct Rx</th>
<th>Indirect Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smania 2009</td>
<td>mCIMT (restraint with cotton mitten) and PT</td>
<td>5 wks</td>
<td>mCIMT: restraint wear, 8hrs/day [56hrs/wk] with PT, 1hr/day for 2 days/wk [2hrs/wk]</td>
<td>Clinician-supervised PT, parents provided restraint at home</td>
<td>PT: 5 wks</td>
<td>1hr/day for 2 days/wk [2hrs/wk]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Total direct Rx (PT): 10hrs</td>
<td></td>
<td>Total indirect Rx (restraint at home): 280hrs</td>
<td></td>
</tr>
<tr>
<td>Taub 2011</td>
<td>CIMT (restraint with long arm, fibreglass, univalved cast and shaping in play and ADLs) and ‘transfer package’/HP</td>
<td>3 wks (excl. weekends): 13 days CIMT, 2 days ‘transfer package’</td>
<td>CIMT: restraint wear and shaping, 6hrs/day for 13 consecutive weekdays [30hrs/wk] ‘Transfer package’/HP: 6hrs/day for 2 consecutive weekdays following CIMT</td>
<td>Clinician-supervised and HP, training by parents at home or teachers at school</td>
<td>OT and/or PT: 24 wks</td>
<td>Varied from 1-2hrs/wk</td>
</tr>
<tr>
<td>Aarts 2010</td>
<td>mCIMT-BiT (restraint with fabric sling and shaping and repetitive task practice, followed by BiT without restraint) and HP</td>
<td>8 wks: 6 wks mCIMT, 2 wks BiT</td>
<td>mCIMT-BiT: restraint wear and shaping and repetitive task practice, 3hrs/day for 3 days/wk [9hrs/wk]; mCIMT(i): 1.75hrs/day for 3 days/wk [5.25hrs/wk]; mCIMT(g): 1.25hrs/day for 3 days/wk [3.75hrs/wk]; BiT: bimanual task-specific training, 3hrs/day for 3 days/wk [9hrs/wk]; HP: variable hrs</td>
<td>Clinician-supervised and HP</td>
<td>OT and/or PT: 8 wks</td>
<td>OT and/or PT: 1.5hrs/wk</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Total direct Rx (mCIMT): 54hrs [31.5hrs(i); 22.5hrs(g)]</td>
<td></td>
<td>Total indirect Rx (HP): ?hrs</td>
<td></td>
</tr>
<tr>
<td>Sung 2005</td>
<td>FUT with short-arm plaster cast</td>
<td>6 wks</td>
<td>FUT: casting, ?hrs/day [?hrs/wk] with OT, 2x/wk [?hrs/wk]</td>
<td>Clinician-supervised</td>
<td>OT: 6 wks</td>
<td>0.5hr/day for 2 days/wk</td>
</tr>
<tr>
<td>Willis 2002</td>
<td>FUT with long-arm plaster cast</td>
<td>4 wks</td>
<td>FUT: casting, ?hrs/day [?hrs/wk]</td>
<td>Clinician-supervised</td>
<td>Control period prior to FUT</td>
<td>4 wks</td>
</tr>
</tbody>
</table>
Table 2.2. (continued)
Content of intervention, method of delivery and dosage of included randomised controlled trials.

<table>
<thead>
<tr>
<th>Occupational therapy (OT) supplemented with BoNT-A</th>
<th>Content of intervention</th>
<th>Method of delivery</th>
<th>Dosage</th>
<th>Clinician-supervised and HP</th>
<th>OT</th>
<th>Total direct Rx (OT)</th>
<th>Total indirect Rx (HP)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Olesch 2010</strong> OT and BoNT-A</td>
<td>BoNT-A: 3 series of BoNT-A injections in 16wk cycles Dilution: 10U Botox®/0.1mL</td>
<td>OT: 2hrs/wk Mean total dose (BoNT-A): 7.5U Botox®/kg/bw Total direct Rx (OT): 12hrs Total indirect Rx (HP): ?hrs</td>
<td>Clinician-supervised and HP</td>
<td>OT</td>
<td>6 wks</td>
<td>2hrs/wk</td>
<td>Total dose direct Rx (OT): 12hrs</td>
</tr>
<tr>
<td><strong>Lowe 2006</strong> OT and BoNT-A</td>
<td>OT: 1 x 1.5hr session and 6 x 0.75hr sessions BoNT-A: Group 1 series of BoNT-A injections at baseline Dilution: 100U Botox®/0.5mL Mean total dose (BoNT-A): 8U Botox®/kg/bw Total direct Rx (OT): 6hrs Total indirect Rx (HP): ?hrs</td>
<td>Clinician-supervised and HP</td>
<td>OT</td>
<td>4 wks</td>
<td>1 x 0.5hr session and 6 x 0.75hr sessions</td>
<td>Total direct Rx (OT): 5hrs</td>
<td></td>
</tr>
<tr>
<td><strong>Fehlings 2000</strong> OT and BoNT-A</td>
<td>OT: minimum 1 session/2 wks BoNT-A injections: 1 set of BoNT-A injections at baseline Dilution: ?U Botox®/?mL Mean total dose: 4.1U Botox®/kg/bw Total direct Rx (OT): ?hrs</td>
<td>Clinician-supervised</td>
<td>OT</td>
<td>Minimum 1 session/2 wks</td>
<td>Total direct Rx (OT): ?hrs</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Key:** RCT indicates randomised controlled trial; HP, home program; CIMT, constraint induced movement therapy; mCIMT, modified constraint induced movement therapy; mCIMT(i), modified constraint induced movement therapy in an individual setting; mCIMT(g), modified constraint induced movement therapy in a group setting; mCIMT-BiT, modified constraint induced movement therapy combined with bimanual task-specific training; ecoCIMT, ecological approach of constraint induced movement therapy; HABIT, hand-arm bimanual intensive therapy; HABIT(i), hand-arm bimanual intensive therapy in an individual setting; HABIT(g), hand-arm bimanual intensive therapy in a group setting; ES, electrical stimulation; BoNT-A, botulinum toxin A (Botox®, Allergan); FUT, forced-use therapy; OT, occupational therapy; BOT, bimanual occupational therapy; UL, upper limb; ADLs, activities of daily living; kg/bw, kilogram body weight; mth, month(s); wk, week(s); hr, hour(s); U, units; ?, unknown.
## Table 2.3.
**Evaluation of methodological quality of included systematic reviews: PRISMA.**

<table>
<thead>
<tr>
<th>Study intervention</th>
<th>Item score</th>
<th>Total Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dong 2013</td>
<td>1 1 1 1 0 1 1 1 1 0 0 1 0 1 1 0 0 1 0 1 0 1 0</td>
<td>17</td>
</tr>
<tr>
<td>Hoare 2009</td>
<td>1 1 1 0 1 1 1 1 1 1 1 0 0 1 1 1 1 0 0 0 1 0 1 0</td>
<td>18</td>
</tr>
<tr>
<td>Huang 2009</td>
<td>1 1 1 1 0 1 0 1 1 0 1 1 1 0 0 1 1 1 1 0 1 1 1 0</td>
<td>19</td>
</tr>
<tr>
<td>Other UL interventions</td>
<td>1 1 1 1 0 1 1 1 1 1 1 1 0 1 1 1 1 1 0 1 1 1 1 1</td>
<td>24</td>
</tr>
<tr>
<td>Case-Smith 2013</td>
<td>1 1 1 1 1 0 1 0 0 0 0 0 0 1 0 0 0 0 0 1 1 0 0</td>
<td>12</td>
</tr>
<tr>
<td>Morgan 2013</td>
<td>1 1 1 1 0 1 1 1 1 1 1 0 1 1 0 1 1 1 1 0 1 1 1 1</td>
<td>21</td>
</tr>
</tbody>
</table>

**Signature or modified constraint induced movement therapy (CIMT, mCIMT) or forced use therapy (FUT)**

**Scale of item score:** 0 = absent, 1 = present.


**Key:** CIMT, constraint induced movement therapy; mCIMT, modified constraint induced movement therapy; FUT, forced use therapy; UL, upper limb.
## Table 2.4.
Evaluation of methodological quality of included randomised controlled trials: Downs and Black Scale.

<table>
<thead>
<tr>
<th>Study</th>
<th>Item Score</th>
<th>Total Score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Signature constraint induced movement therapy (CIMT)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deluca 2006</td>
<td>1 0 1 1 0 1 1 0</td>
<td>1 0 0 0 0 0</td>
</tr>
<tr>
<td>Taub 2004</td>
<td>1 1 1 1 1 1 1 0 0 1 0 0 0 0 0</td>
<td>1 1 1 1 1 1 1 0 1 0 1 0 0 0 0</td>
</tr>
<tr>
<td><strong>Modified constraint induced movement therapy (mCIMT)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gelkop 2014</td>
<td>1 1 1 1 1 1 1 1 1 1 1 1 1 0 0</td>
<td>0 1 1 1 1 1 1 1 0 1 1 0 1 1 1 1 0</td>
</tr>
<tr>
<td>Hoare 2013</td>
<td>1 1 1 1 1 1 1 1 1 1 1 1 1 0 0</td>
<td>0 1 1 1 1 1 1 1 1 1 1</td>
</tr>
<tr>
<td>XU 2011</td>
<td>1 1 1 1 1 1 1 1 1 1 1 1 1 0 0</td>
<td>0 1 1 1 1 1 1 1 1 1 1 0 0 1 1 1</td>
</tr>
<tr>
<td>Al-Oraibi 2011</td>
<td>1 1 1 1 0 1 1 0 1 1 0 0 0 0 0</td>
<td>0 1 1 1 1 0 1 1 0 1 1 0 1 0 0 0 0 0</td>
</tr>
<tr>
<td>Eliasson 2011</td>
<td>1 1 1 1 0 1 1 0 1 1 0 0 0 0 0</td>
<td>0 1 1 1 1 1 0 1 1 0 1 0 0 0 0 0 0 0</td>
</tr>
<tr>
<td>Fedrizzi 2013</td>
<td>1 1 1 1 1 1 1 1 1 1 1 1 1 0 0</td>
<td>0 0 0 1 1 1 1 1 1 1 1 0 0 1 1 1</td>
</tr>
<tr>
<td>Wallen 2011</td>
<td>1 1 1 1 0 1 1 1 1 1 0 0 0 0 0</td>
<td>0 1 1 1 1 1 1 1 1 1 1</td>
</tr>
<tr>
<td>Smania 2009</td>
<td>1 1 1 1 1 0 1 1 1 1 1 1 0 0 0</td>
<td>0 1 1 1 1 1 1 0 1 1 1 0 1 1 1</td>
</tr>
<tr>
<td><strong>Hybrid CIMT</strong></td>
<td></td>
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</tr>
<tr>
<td>Taub 2011</td>
<td>1 1 1 1 0 1 1 0 1 1 0 0 0 0 0</td>
<td>0 1 1 1 1 1 1 1 1 1 1</td>
</tr>
<tr>
<td>Aarts 2010</td>
<td>1 1 1 1 1 0 1 1 0 1 1 0 0 0 0 1 1 1 1 1 1 1 1 1</td>
<td>0 1 0 0 0 1 1 1</td>
</tr>
<tr>
<td><strong>Forced use therapy (FÜT)</strong></td>
<td></td>
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<tr>
<td>Sung 2005</td>
<td>1 1 1 1 0 1 1 1 1 1 1 0 1 0 0 0 0 0 0 0 1 1 1 1 1 1 1 1 0 1 0 1 0 0 0</td>
<td>17</td>
</tr>
<tr>
<td>Willis 2002</td>
<td>1 0 1 1 1 1 1 1 1 1 1 0 0 0 0 0 0 0 0 1 1 1 1 1 1 1 1 1 0 1 0 0 1 0 0 0 0</td>
<td>14</td>
</tr>
<tr>
<td><strong>Occupational therapy (OT) supplemented with BoNT-A</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Olesch 2010</td>
<td>1 1 1 1 0 1 1 1 1 1 1 1 1 0 0 0 0 0 0 1 1 1 1 1 1 1 1 1 0 1 1 1</td>
<td>20</td>
</tr>
<tr>
<td>Lowe 2006</td>
<td>1 1 1 1 1 1 1 1 1 1 1 0 0 0 0 1 1 1 1 1 1</td>
<td>1 1 1</td>
</tr>
<tr>
<td>Fehlings 2000</td>
<td>1 1 1 1 0 1 1 1 1 1 1 1 1 0 0 0 0 1 1 1 1 1</td>
<td>1 1 1</td>
</tr>
</tbody>
</table>

Scale of item score: 0 = no, unable to determine, or partially; 1 = yes.
The **Downs and Black Scale criteria** are: (1) Hypothesis/aim/objective; (2) Description of main outcomes; (3) Subject characteristics; (4) Interventions; (5) Principal confounders; (6) Main findings; (7) Estimates of random variability; (8) Adverse events; (9) Reporting losses to follow-up; (10) Reporting of main outcomes; (11) Representativeness of recruited sample; (12) Representativeness of included sample; (13) Representativeness of study location; (14) Subject blinding; (15) Assessor blinding; (16) Retrospective subgroup analyses; (17) Follow-up time period; (18) Statistical analysis; (19) Compliance with interventions; (20) Validity and reliability of outcome measures; (21) Sample population; (22) Recruitment time period; (23) Randomisation; (24) Concealed allocation; (25) Intention to treat; (26) Proportion of sample lost to follow-up; (27) Power calculation for primary outcome; (28) Adequately powered sample size to detect clinically meaningful change.
Table 2.5. Summary of upper limb motor activity outcomes and effect sizes for included randomised controlled trials.

<table>
<thead>
<tr>
<th>Study</th>
<th>UL treatment vs control</th>
<th>UL activity outcome</th>
<th>Treatment Mean (SD)</th>
<th>N</th>
<th>Control Mean (SD)</th>
<th>N</th>
<th>Post-treatment Assessment (wks)</th>
<th>Treatment Mean (SD)</th>
<th>N</th>
<th>Control Mean (SD)</th>
<th>N</th>
<th>Post-treatment ES</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Signature constraint induced movement therapy (CIMT) vs Control</strong></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Taub 2004</td>
<td>CIMT vs usual care</td>
<td>PMAL (amount of use)</td>
<td>0.8 (0.4)</td>
<td>9</td>
<td>1.1 (0.8)</td>
<td>9</td>
<td>Post 3</td>
<td>2.8 (1.1)</td>
<td>9</td>
<td>1.2 (0.8)</td>
<td>9</td>
<td>1.66</td>
<td>0.53 to 2.64</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Taub 2004</td>
<td>CIMT vs usual care</td>
<td>PMAL (quality of use)</td>
<td>0.9 (0.6)</td>
<td>9</td>
<td>1.6 (1.2)</td>
<td>9</td>
<td>Post 3</td>
<td>2.7 (1.0)</td>
<td>9</td>
<td>1.9 (1.1)</td>
<td>9</td>
<td>0.76</td>
<td>-0.23 to 1.68</td>
<td>0.13</td>
</tr>
<tr>
<td><strong>Modified constraint induced movement therapy (mCIMT) vs Control</strong></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Gelkop 2014</td>
<td>mCIMT vs HABIT</td>
<td>AHA</td>
<td>47.3 (6.7)</td>
<td>6</td>
<td>43.0 (4.0)</td>
<td>6</td>
<td>Post 8</td>
<td>59.0 (6.0)</td>
<td>6</td>
<td>52.5 (4.8)</td>
<td>6</td>
<td>1.20</td>
<td>-0.11 to 2.32</td>
<td>0.07</td>
</tr>
<tr>
<td>Al-Oraibi 2011</td>
<td>mCIMT vs NDT</td>
<td>AHA</td>
<td>41.6 (12.6)</td>
<td>7</td>
<td>56.0 (18.8)</td>
<td>7</td>
<td>Post 8</td>
<td>48.0 (11.7)</td>
<td>7</td>
<td>56.6 (18.7)</td>
<td>7</td>
<td>-0.55</td>
<td>-1.58 to 0.55</td>
<td>-0.32</td>
</tr>
<tr>
<td>Ellasson 2011</td>
<td>mCIMT vs usual care</td>
<td>AHA</td>
<td>53.0 (10.0)</td>
<td>12</td>
<td>45.0 (21.0)</td>
<td>13</td>
<td>Post 8</td>
<td>59.0 (9.0)</td>
<td>12</td>
<td>46 (21.0)</td>
<td>13</td>
<td>0.79</td>
<td>-0.05 to 1.58</td>
<td>0.06</td>
</tr>
<tr>
<td>Wallen 2011</td>
<td>mCIMT vs OT</td>
<td>AHA</td>
<td>60.6 (29.8)</td>
<td>25</td>
<td>49.8 (30.8)</td>
<td>25</td>
<td>Post 10</td>
<td>62.9 (29.3)</td>
<td>25</td>
<td>52 (28.9)</td>
<td>25</td>
<td>0.37</td>
<td>-0.19 to 0.93</td>
<td>0.19</td>
</tr>
<tr>
<td>Wallen 2011</td>
<td>mCIMT vs OT</td>
<td>PMAL-R (amount of use)</td>
<td>47.1 (17.3)</td>
<td>25</td>
<td>38.7 (15.8)</td>
<td>25</td>
<td>Post 10</td>
<td>57.5 (20.0)</td>
<td>25</td>
<td>51.5 (17.3)</td>
<td>25</td>
<td>0.32</td>
<td>-0.24 to 0.87</td>
<td>0.26</td>
</tr>
<tr>
<td>Wallen 2011</td>
<td>mCIMT vs OT</td>
<td>PMAL-R (quality of use)</td>
<td>42.4 (21.7)</td>
<td>25</td>
<td>38.4 (17.3)</td>
<td>25</td>
<td>Post 10</td>
<td>59.6 (23.6)</td>
<td>25</td>
<td>51.3 (19.7)</td>
<td>25</td>
<td>0.38</td>
<td>-0.18 to 0.94</td>
<td>0.18</td>
</tr>
<tr>
<td>Gelkop 2014</td>
<td>mCIMT vs HABIT</td>
<td>QUEST (total)</td>
<td>55.0 (8.0)</td>
<td>6</td>
<td>56.8 (7.8)</td>
<td>6</td>
<td>Post 8</td>
<td>74.0 (4.0)</td>
<td>6</td>
<td>70.4 (9.6)</td>
<td>6</td>
<td>0.49</td>
<td>-0.69 to 1.60</td>
<td>0.42</td>
</tr>
<tr>
<td>Fedrizi 2013</td>
<td>mCIMT vs usual care</td>
<td>QUEST (total)</td>
<td>69.4 (15.8)</td>
<td>39</td>
<td>72.2 (17.2)</td>
<td>33</td>
<td>Post 10</td>
<td>76.3 (14.9)</td>
<td>39</td>
<td>72.6 (17.7)</td>
<td>33</td>
<td>0.23</td>
<td>-0.24 to 0.69</td>
<td>0.34</td>
</tr>
<tr>
<td>Fedrizi 2013</td>
<td>mCIMT and intensive UT</td>
<td>Besta Scale (global)</td>
<td>2.4 (0.8)</td>
<td>39</td>
<td>2.6 (0.8)</td>
<td>33</td>
<td>Post 10</td>
<td>2.6 (0.8)</td>
<td>39</td>
<td>2.7 (0.8)</td>
<td>33</td>
<td>-0.13</td>
<td>-0.59 to 0.34</td>
<td>-0.60</td>
</tr>
<tr>
<td><strong>Hybrid CIMT vs Control</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smania 2009</td>
<td>mCIMT vs PT</td>
<td>PAUT</td>
<td>5.0 (5.0)</td>
<td>5</td>
<td>15.0 (6.0)</td>
<td>5</td>
<td>Post 5</td>
<td>20.0 (13.0)</td>
<td>5</td>
<td>10.0 (5.0)</td>
<td>5</td>
<td>1.02</td>
<td>-0.39 to 2.22</td>
<td>0.15</td>
</tr>
<tr>
<td>Aarts 2010</td>
<td>Hybrid CIMT vs usual care</td>
<td>AHA</td>
<td>53.3 (14.6)</td>
<td>28</td>
<td>50.6 (22.5)</td>
<td>22</td>
<td>Post 8</td>
<td>60.1 (15.3)</td>
<td>28</td>
<td>53.1 (22.2)</td>
<td>22</td>
<td>0.38</td>
<td>-0.19 to 0.93</td>
<td>0.19</td>
</tr>
<tr>
<td>Aarts 2010</td>
<td>Hybrid CIMT vs usual care</td>
<td>ABILHAND-Kids</td>
<td>20.9 (5.1)</td>
<td>28</td>
<td>22.6 (6.9)</td>
<td>22</td>
<td>Post 8</td>
<td>28.4 (5.9)</td>
<td>28</td>
<td>23.7 (6.0)</td>
<td>22</td>
<td>0.79</td>
<td>0.20 to 1.36</td>
<td>0.01</td>
</tr>
<tr>
<td>Taub 2011</td>
<td>Hybrid CIMT vs usual care</td>
<td>PMAL</td>
<td>1.3 (0.6)</td>
<td>10</td>
<td>1.3 (0.3)</td>
<td>10</td>
<td>Post 3</td>
<td>3.5 (0.6)</td>
<td>10</td>
<td>1.4 (0.5)</td>
<td>10</td>
<td>3.80</td>
<td>2.21 to 5.07</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Taub 2011</td>
<td>Hybrid CIMT vs usual care</td>
<td>INMAP</td>
<td>29.5 (7.1)</td>
<td>10</td>
<td>27.6 (6.6)</td>
<td>10</td>
<td>Post 3</td>
<td>35.9 (6.2)</td>
<td>10</td>
<td>27.8 (6.6)</td>
<td>10</td>
<td>1.27</td>
<td>0.26 to 2.17</td>
<td>0.01</td>
</tr>
<tr>
<td>Taub 2011</td>
<td>Hybrid CIMT vs usual care</td>
<td>PAFT (impaired arm use)</td>
<td>11.9 (8.0)</td>
<td>10</td>
<td>14.4 (12.2)</td>
<td>10</td>
<td>Post 3</td>
<td>45.0 (32.6)</td>
<td>10</td>
<td>15.0 (12.9)</td>
<td>10</td>
<td>1.21</td>
<td>0.21 to 2.11</td>
<td>0.01</td>
</tr>
<tr>
<td>Taub 2011</td>
<td>Hybrid CIMT vs usual care</td>
<td>PAFT (functional ability)</td>
<td>2.3 (0.4)</td>
<td>10</td>
<td>2.2 (0.5)</td>
<td>10</td>
<td>Post 3</td>
<td>2.6 (0.4)</td>
<td>10</td>
<td>2.1 (0.6)</td>
<td>10</td>
<td>0.98</td>
<td>0.02 to 1.86</td>
<td>0.04</td>
</tr>
</tbody>
</table>

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### Table 2.5. (continued)
Summary of upper limb motor activity outcomes and effect sizes for included randomised controlled trials.

<table>
<thead>
<tr>
<th>Forced use therapy (FUT) vs Control</th>
<th>Sung 2005</th>
<th>FUT vs OT</th>
<th>WeeFIM (self-care)</th>
<th>(continued)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sung 2005</td>
<td>FUT vs OT</td>
<td>BBT (impaired UL)</td>
<td>8.2 (5.0)</td>
</tr>
<tr>
<td></td>
<td>Sung 2005</td>
<td>FUT vs OT</td>
<td>EDPA</td>
<td>6.9 (1.4)</td>
</tr>
<tr>
<td>Occupational therapy (OT) supplemented with BoNT-A vs Control</td>
<td>Olesch 2010</td>
<td>OT vs BoNT-A</td>
<td>PDMS-FM (standardised scores)</td>
<td>503.6 (25.8)</td>
</tr>
<tr>
<td></td>
<td>Lowe 2006</td>
<td>OT vs BoNT-A</td>
<td>PEDI (self-care, caregiver assistance)</td>
<td>26.2 (10.5)</td>
</tr>
<tr>
<td></td>
<td>Lowe 2006</td>
<td>OT vs BoNT-A</td>
<td>PEDI (self-care, functional skills)</td>
<td>50.7 (13.7)</td>
</tr>
<tr>
<td></td>
<td>Olesch 2010</td>
<td>OT vs BoNT-A</td>
<td>QUEST (total)</td>
<td>75.4 (8.6)</td>
</tr>
<tr>
<td></td>
<td>Lowe 2006</td>
<td>OT vs BoNT-A</td>
<td>QUEST (total)</td>
<td>32.1 (11.0)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>N</th>
<th>Post 6</th>
<th>SD</th>
<th>ES</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>18</td>
<td>25.4 (5.8)</td>
<td>18</td>
<td>21.2 (8.7)</td>
<td>13</td>
</tr>
<tr>
<td>18</td>
<td>10.5 (5.7)</td>
<td>18</td>
<td>9.5 (7.1)</td>
<td>13</td>
</tr>
<tr>
<td>18</td>
<td>7.6 (1.7)</td>
<td>18</td>
<td>7.1 (1.4)</td>
<td>13</td>
</tr>
<tr>
<td>11</td>
<td>519.6 (25.3)</td>
<td>11</td>
<td>513.1 (33.8)</td>
<td>11</td>
</tr>
<tr>
<td>21</td>
<td>28.2 (8.2)</td>
<td>21</td>
<td>23.6 (11.0)</td>
<td>21</td>
</tr>
<tr>
<td>21</td>
<td>53.1 (11.5)</td>
<td>21</td>
<td>44.2 (13.3)</td>
<td>21</td>
</tr>
<tr>
<td>21</td>
<td>76.3 (13.2)</td>
<td>21</td>
<td>70.8 (12.8)</td>
<td>11</td>
</tr>
<tr>
<td>21</td>
<td>43.9 (15.1)</td>
<td>21</td>
<td>36.0 (12.4)</td>
<td>21</td>
</tr>
</tbody>
</table>

Key: UL, upper limb; CIMT, signature constraint induced movement therapy; mCIMT, modified constraint induced movement therapy; HABIT, hand-arm bimanual intensive therapy; NDT, neurodevelopmental therapy; OT, occupational therapy; PT, physiotherapy; FUT, forced use therapy; BoNT-A, intramuscular UL injections of botulinum toxin A; PMAL, pediatric motor activity log; PMAL-R, revised pediatric motor activity log; AHA, assisting hand assessment; QUEST, quality of upper extremity skills test; PAUT, paretic arm use test; INMAP, inventory of new motor activities and programs instrument; PAFT, pediatric arm function test; WeeFIM, paediatric version of the functional independence measure; BBT, box and blocks test; EDPA, erhardt developmental prehension assessment; PDMS-FM, peabody developmental motor scales - fine motor subscale; PEDI, pediatric evaluation of disability inventory; SD, standard deviation; ES, effect size; 95% CI, 95% confidence interval.
Appendix 2.1.
This search strategy was used for Pubmed and adapted for each database. It is comprised of the following key words and controlled vocabulary terms (i.e. MeSH headings) where available:

1. "Infant"[Mesh] OR "Child, preschool"[Mesh] OR Infant* OR baby OR babies OR neonate* OR newborn* OR "preschool child" OR "preschool children"
   AND
   AND
3. "Therapeutics"[Mesh] OR "Rehabilitation"[Mesh] OR therapeutics OR rehabilitation OR intervention* OR treatment* OR therapy OR therapies OR "Occupational Therapy"[Mesh] OR "Physical Therapy"[Mesh] OR "Splints"[Mesh] OR "Casts, surgical"[Mesh] OR "occupational therapy" OR "physical therapy" OR physiotherapy OR "functional training" OR "constraint induced therapy" OR "constraint-induced therapy" OR "constraint induced movement therapy" OR "forced use treatment" OR "forced use therapy" OR "bimanual training" OR "bimanual therapy" OR "motor learning" OR "Neurodevelopmental treatment" OR "Neurodevelopmental therapy" OR "Bobath" OR "task oriented training" OR "task oriented therapy" OR "action observation therapy" OR "action observation training" OR "mirror therapy" OR "mirror neuron therapy" OR "mirror neurone therapy" OR "splint*" OR "cast*" OR "conductive education" OR "developmental therapy"
   AND
4. "Randomized Controlled trials as Topic"[Mesh] OR "Cross-over Studies"[Mesh] OR "Single-blind Method"[Mesh] OR "Double-blind Method"[Mesh] OR "randomized controlled trial*" OR "randomised controlled trial*" OR "randomized crossover trial*" OR "randomised crossover trial*" OR "crossover procedure" OR "cross-over study" OR "cross-over studies" OR "crossover design" OR "crossover trial*" OR "single blind procedure" OR "single blind" OR "single blind method" OR "single blind study" OR "single blind studies" OR "double blind procedure" OR "double blind" OR "double blind method" OR "double blind study" OR "double blind studies" OR "systematic review" OR "Meta-Analysis [Publication Type]"[Mesh] OR "Meta-Analysis as Topic"[Mesh] OR "Meta-analysis" OR "meta-analysis"
   AND
Appendix 2.2.
Study design, participant demographics and methods of included systematic reviews.

<table>
<thead>
<tr>
<th>Review</th>
<th>Intervention</th>
<th>Population</th>
<th>Included randomised controlled trials</th>
<th>Meta-analysis?</th>
<th>Clinical Inference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Signature constraint induced movement therapy</strong> (CIMT) and/or modified CIMT (mCIMT) and/or forced use therapy (FUT)**</td>
<td><strong>Dong 2013</strong> mCIMT, bimanual training</td>
<td>CH (2-16 yrs)</td>
<td>1 of 6 RCTs met criteria for inclusion in this review</td>
<td>No</td>
<td>High-level evidence for efficacy of both CIMT and bimanual training to improve impaired UL function and overall functional performance. CIMT is more effective in improving impaired UL function compared to bimanual training; bimanual training is more effective in improving performance in bimanual and functional tasks compared to CIMT. Methodological limitations included variability in protocols of bimanual training across studies. Significant treatment effect using mCIMT in a single trial. Positive trend favouring CIMT and FUT; CIMT, mCIMT and FUT are recommended to remain within clinical trials until evidence is clearer.</td>
</tr>
<tr>
<td></td>
<td><strong>Hoare 2009</strong> CIMT, mCIMT, FUT</td>
<td>CH (0-19 yrs)</td>
<td>1 of 2 RCTs met criteria for inclusion in this review</td>
<td>No</td>
<td>Unclear if dose of intervention or constraint has an effect on use of the impaired UL. Critical dose intensity is unclear.</td>
</tr>
<tr>
<td></td>
<td><strong>Huang 2009</strong> CIMT, FUT</td>
<td>CH (1 mth-18 yrs)</td>
<td>3 of 5 RCTs met criteria for inclusion in this review</td>
<td>No</td>
<td>Positive short-term effects found for developmental interventions, with limited evidence for long-term effects. Inconclusive evidence for NDT. Positive effects for interventions specifically designed for children with CP. Motor interventions that produced significant changes in motor performance incorporated meaningful play activities, family collaboration, functional goals and social elements. Positive effects found for OT interventions that embedded behavioural and learning principles.</td>
</tr>
<tr>
<td><strong>Occupational therapy (OT)</strong></td>
<td><strong>Case-Smith 2013</strong> Developmental interventions</td>
<td>CP or at risk of DD, including CH (0-5 yrs)</td>
<td>5 of 12 RCTs met criteria for inclusion in this review</td>
<td>No</td>
<td>Positive short-term effects found for developmental interventions, with limited evidence for long-term effects. Inconclusive evidence for NDT. Positive effects for interventions specifically designed for children with CP. Motor interventions that produced significant changes in motor performance incorporated meaningful play activities, family collaboration, functional goals and social elements. Positive effects found for OT interventions that embedded behavioural and learning principles.</td>
</tr>
<tr>
<td><strong>Environmental Enrichment (EE)</strong></td>
<td><strong>Morgan 2013</strong> Environmental enrichment (motor, sensory, social), parent coaching</td>
<td>At high risk of CP or with CP, including CH (0-94 mths)</td>
<td>3 of 7 RCTs met criteria for inclusion in this review</td>
<td>Yes</td>
<td>High-level evidence for a small positive effect of EE to improve motor outcomes. Methodological limitations across studies included inadequate descriptions of standard care interventions and inconsistent definitions of EE.</td>
</tr>
</tbody>
</table>

Appendix 2.2. (continued)
Study design, participant demographics and methods of included systematic reviews.
Intensive NDT and casting, regular NDT and casting, BoNT-A alone, BoNT-A and OT, signature CIMT, eco-CIMT, mCIMT, mCIMT and FES, hybrid CIMT, FUT, HABIT, OT home programs, splinting

CH (0-18 yrs) 22 of 42 RCTs met criteria for inclusion in this review

Strong evidence for efficacy of goal-directed OT home programs to improve UL outcomes. Modest evidence to support intensive, activity-based, goal-directed interventions such as CIMT and BIT as more effective approaches than standard care to improve UL outcomes. Paucity of evidence for efficacy of block therapy alone due to insufficient dosage to achieve sustained improvements in UL outcomes. Goal-directed OT home programs may supplement hands-on direct therapy for increased dosage of OT. Further investigation is required to determine: optimum mode and dose of UL training supplemented with BoNT-A; critical threshold dosage of UL interventions; efficacy of UL interventions for infants; characteristics of children who achieve clinically meaningful outcomes post-treatment.

Key: UL, upper limb; SR, systematic review; RCT, randomised controlled trial; CH, congenital hemiplegia; CP, cerebral palsy; DD, developmental disorders; CIMT, constraint induced movement therapy; mCIMT, modified constraint induced movement therapy; FUT, forced-use therapy; OT, occupational therapy; NDT, neurodevelopmental treatment; HABIT, hand-arm bimanual intensive therapy; NDT, neurodevelopmental treatment; BoNT-A, intramuscular UL injections of botulinum toxin A; EE, environmental enrichment; FES, functional electrical stimulation.
Appendix 2.3.
Compliance with interventions and participant retention of included randomised controlled trials.

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Number of participants who completed treatment/ Number who received treatment (%)</th>
<th>Number of participants retained/ Number who received treatment (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deluca 2006</td>
<td>Signature CIMT</td>
<td>9/9 completed (100%) / 9/9 retained (100%)</td>
<td></td>
</tr>
<tr>
<td>Taub 2004</td>
<td>Signature CIMT</td>
<td>9/9 completed (100%) / 9/9 retained (100%)</td>
<td></td>
</tr>
<tr>
<td>Gelkop 2014</td>
<td>(i) mCIMT</td>
<td>6/6 completed (100%) / 6/6 retained (100%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(ii) HABIT</td>
<td>6/6 completed (100%) / 6/6 retained (100%)</td>
<td></td>
</tr>
<tr>
<td>Al-Oraibi 2011</td>
<td>mCIMT</td>
<td>7/10 completed (70%) / 7/10 retained (70%)</td>
<td></td>
</tr>
<tr>
<td>Eliasson 2011</td>
<td>eco-CIMT</td>
<td>14/18 completed (78%) / 14/18 retained (78%)</td>
<td></td>
</tr>
<tr>
<td>Wallen 2011</td>
<td>mCIMT</td>
<td>25/25 completed (100%) / 25/25 retained (100%)</td>
<td></td>
</tr>
<tr>
<td>Smania 2009</td>
<td>mCIMT</td>
<td>5/5 completed (100%) / 5/5 retained (100%)</td>
<td></td>
</tr>
<tr>
<td>Sung 2005</td>
<td>mCIMT</td>
<td>18/18 completed (100%) / 18/18 retained (100%)</td>
<td></td>
</tr>
<tr>
<td>Hoare 2013</td>
<td>mCIMT and BoNT-A</td>
<td>17/17 completed (100%) / 17/17 retained (100%)</td>
<td></td>
</tr>
<tr>
<td>Xu 2012</td>
<td>(i) mCIMT</td>
<td>23/25 completed (92%) / 23/25 retained (92%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(ii) mCIMT and ES</td>
<td>23/24 completed (96%) / 22/24 retained (92%)</td>
<td></td>
</tr>
<tr>
<td>Fedrizzi 2013</td>
<td>(i) mCIMT</td>
<td>39/39 completed (100%) / 39/39 retained (100%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(ii) Bimanual intensive rehabilitation program</td>
<td>33/33 completed (100%) / 32/33 retained (97%)</td>
<td></td>
</tr>
<tr>
<td>Taub 2011</td>
<td>mCIMT and ‘transfer package’</td>
<td>10/10 completed (100%) / 9/10 retained (90%)</td>
<td></td>
</tr>
<tr>
<td>Aarts 2010</td>
<td>mCIMT-BiT</td>
<td>28/28 completed (100%) / 28/28 retained (100%)</td>
<td></td>
</tr>
<tr>
<td>Willis 2002</td>
<td>FUT</td>
<td>12/12 completed (100%) / 7/12 retained (58%)</td>
<td></td>
</tr>
<tr>
<td>Olesch 2010</td>
<td>OT supplemented with BoNT-A</td>
<td>11/11 completed (100%) / 11/11 retained (100%)</td>
<td></td>
</tr>
<tr>
<td>Lowe 2006</td>
<td>OT supplemented with BoNT-A</td>
<td>21/21 completed (100%) / 21/21 retained (100%)</td>
<td></td>
</tr>
<tr>
<td>Fehlings 2000</td>
<td>OT supplemented with BoNT-A</td>
<td>15/15 completed (100%) / 14/15 retained (93%)</td>
<td></td>
</tr>
</tbody>
</table>

Key: CIMT, constraint induced movement therapy; mCIMT, modified constraint induced movement therapy; mCIMT-BiT, modified constraint-induced movement therapy combined with bimanual task-specific training; eco-CIMT, ecological approach of constraint induced movement therapy; HABIT, hand-arm bimanual intensive therapy; ES, electrical stimulation; BoNT-A, intramuscular upper limb injections of botulinum toxin A; FUT, forced-use therapy; OT, occupational therapy; %, percentage.
### Appendix 2.4.
**Adverse events related to interventions of included randomised controlled trials.**

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention vs Control</th>
<th>Number of participants/ Number in treatment group or control group (%)</th>
<th>Mild</th>
<th>Number of participants for each adverse event related to intervention based on severity:</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taub 2004</td>
<td>Signature CIMT (intervention)</td>
<td>4/9 mild (44%)</td>
<td>4 with mild skin redness, rash or pinching</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Usual care (control)</td>
<td>0/9 (0%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hoare 2013</td>
<td>mCIMT and BoNT-A (intervention)</td>
<td>1/17 mild (6%)</td>
<td>1 with temporary soreness at injection site after BoNT-A</td>
<td>6 with excessive grip weakness after BoNT-A</td>
<td>1 with vomiting post-sedation</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>BOT and BoNT-A (control)</td>
<td>0/17 (0%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Olesch 2010</td>
<td>OT supplemented with BoNT-A (intervention)</td>
<td>1/11 mild (9%)</td>
<td>1 with rash after BoNT-A</td>
<td>1 with temporary finger weakness after BoNT-A</td>
<td>1 with prolonged finger weakness after BoNT-A</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>OT (control)</td>
<td>0/11 (0%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lowe 2006</td>
<td>OT supplemented with BoNT-A (intervention)</td>
<td>0/21 (0%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>OT (control)</td>
<td>0/21 (0%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fehlings 2000</td>
<td>OT supplemented with BoNT-A (intervention)</td>
<td>1/14 moderate (7%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Key:** CIMT, constraint induced movement therapy; mCIMT, modified constraint induced movement therapy; BoNT-A, intramuscular upper limb injections of botulinum toxin A; OT, occupational therapy; BOT, bimanual occupational therapy; PT, physiotherapy; %, percentage; NA, not applicable; ?, unknown; NR, none reported.
2.3. Summary and conclusions

Key findings of the systematic review were:

- There is evidence to support the efficacy of modified constraint induced (mCIMT), hybrid CIMT and occupational therapy (OT) supplemented with UL intramuscular Botulinum toxin A (BoNT-A) injections to improve motor function of the impaired UL based on RCTs of school-aged children that included infants (younger than three years) with UCP.
- There is limited evidence to support the efficacy of non-surgical UL interventions for infants (younger than three years) with UCP (9% the total RCT sample).
- There is emerging evidence for environmental enrichment to improve motor outcomes in infants with or at risk of CP.
- Compliance with approaches such as mCIMT, hybrid CIMT and OT supplemented with intramuscular BoNT-A is promising in school-aged children that included infants; however, compliance and safety have not been adequately tested in infants.
- The critical timing, critical and active ingredient(s), dosage and mode of delivery of UL motor interventions to maximize UL function in infants with or at risk of UCP requires more research.

The book chapter summarised in Chapter 1 and the SR presented in this chapter addressed Aim 1 of this doctoral program. As predicted in Hypothesis 1, the SR identified limited evidence for non-surgical UL interventions to improve unimanual and bimanual UL motor function specifically for this young and at-risk population; identifying only one RCT that included participants who were all younger than three years with or at risk of UCP. As the SR identified a paucity of evidence for non-surgical UL interventions for at-risk infants younger than six months C.A., a second search was conducted for studies of at-risk infants younger than three years C.A. These findings confirm the need for more rigorous research to provide clear directions for the efficacy and feasibility of suitable interventions for young infants who are at high risk of UCP.

Furthermore, a literature search (including hand searching and citation tracking) for valid and reliable measures of UL motor development identified limited
evidence for: (i) early detection of UCP in at-risk infants younger than 12 months C.A.; (ii) evaluating and quantifying early abnormalities in UL motor development to predict UCP; and (ii) measuring change in UL function in response to infant-friendly UL motor interventions.

A valid, reliable and quantitative measure of early abnormalities in UL motor behaviours which can be used to predict UCP is therefore required in infants with asymBI during early motor development. This doctoral program contributes to this limited evidence base by presenting the development, validation and reproducibility testing of a new quantitative UL measure, the Grasp and Reach Assessment of Brisbane (GRAB).

The next chapter describes the design and methods of the doctoral program as a component of the larger ARC-funded study, ‘The UP-BEAT Study’; and addresses Aim 2 by including a brief description of the GRAB, as well as the stages of development of the scoring method and criteria of the GRAB. A more detailed description of the development and validation of the GRAB is presented later, to address Aim 2, in Chapter 4.
Chapter 3: Study design and methods

3.1. Introduction

To contribute to the currently limited evidence base of valid and reliable measures of early abnormalities in UL motor development in infants younger than 12 months who are at risk of UCP; this doctoral program primarily focused on the development, validation and reproducibility testing of a new measure of early reach to grasp development for infants with asymBI who are younger than 6 months C.A., called the Grasp and Reach Assessment of Brisbane (GRAB). The GRAB was designed to: (i) detect, quantify and evaluate asymmetries between ULs during early unimanual and bimanual reach and grasp behaviours at 14, 16 and 18 weeks C.A. in infants with asymBI; (ii) identify differences in early unimanual and bimanual reach and grasp behaviours between healthy infants and infants with asymBI at 14, 16 and 18 weeks C.A.; and (iii) examine longitudinal development of reach and grasp behaviours in infants with asymBI, in relation to prediction of delayed motor development in infants with asymBI compared to healthy infants at six and 12 months C.A. on the Bayley Scales of Infant and Toddler Development (BSID III; Aim 4).

This chapter entails the design and methods of the doctoral program, which comprised a component of a larger study funded by the Australian Research Council (ARC), ‘The UP-BEAT Study’. The published protocol paper for the UP-BEAT Study is included as Appendix 9.2. A description of the processes for obtaining ethical approval and the recruitment of infants will first be provided. The inclusion and exclusion criteria, as well as the sample size calculations of the doctoral program, (which were initially based on the RCT) will then be discussed. There was no available evidence to provide guidance on an appropriate sample size required for evaluation of construct validity and predictive validity of the GRAB. A flowchart (Figure 3.1.) is presented to indicate the sample sizes used for each study pertaining to the GRAB (i.e. validity, reproducibility and longitudinal); and justification for each sample is also provided. The development of the GRAB is then discussed briefly (with greater detail provided in Chapter 4), followed by a description of the development of its scoring method and criteria.
In relation to Aim 4, the BSID III is also discussed; including its administration procedure, a summary of its concurrent validity, test-retest reliability and its scoring procedure. Finally, a summary of the statistical analyses performed in each study on the GRAB is presented.

3.2. Ethical approval

This doctoral program was positioned in the context of an RCT, which involved the collection of personal information, medical history information and video-recorded assessments of human participants from an at-risk population, infants with asymmetric brain lesions. Ethical clearance was therefore necessary. Informed consent was obtained from the parents or legal guardians of infants prior to enrolment into the study. Ethical approval was sought from and granted by the Human Research Ethics Committees in Queensland, Australia for: (i) the Royal Children’s Hospital, Brisbane (now the Lady Cilento Children’s Hospital, South Brisbane; HREC/09/QRCH/134); (ii) the Royal Brisbane and Women’s Hospital (HREC/09/QRCH/134); (iii) the Gold Coast Hospital (now the Gold Coast University Hospital; SSA/12/QGC/203); (iv) the Mater Mother’s Hospital [1814MC and 1814MC(RG)]; (v) the Mater Children’s Hospital [1814MC and 1814MC(RG)]; and (vi) The University of Queensland (2009001870). Ethical approval was sought from and granted by the Human Research Ethics Committees in Italy for: (i) Pisa University Hospital (43/2011); (ii) Modena University Hospital (43/2011); and Istituto Di Ricovero e Cura a Carattere Scientifico (IRCCS) Gaslini Institute, Genoa (43/2011). All ethical approval letters and amendment approval letters are included as Appendices 9.4.-9.10.

3.3. Recruitment

Infants with asymBI

Infants and their families were recruited from four hospitals in South-east Queensland, Australia (the former Royal Children’s Hospital, Brisbane; Royal Brisbane and Women’s Hospital; Mater Mother’s Hospital; and the former Gold Coast Hospital), living within a 200-km radius of the Royal Brisbane and Women’s Hospital; and from three hospitals in Italy (Pisa University Hospital, Modena University Hospital and IRCCS Gaslini Institute, Genoa).
**Healthy infants**

Infants and their families were recruited in south-east Queensland, Australia through convenience sampling (the former Royal Children’s Hospital, Brisbane; The University of Queensland; and The Brisbane Pregnancy, Babies and Children’s Expo) within a 200-km radius of the Royal Brisbane and Women’s Hospital.

### 3.4. Inclusion and exclusion criteria

**Infants with asymBI**

Infants with asymBI were eligible for inclusion if they: were aged between 0 and 9 weeks C.A. at time of enrollment; presented with clinical signs of a unilateral (one sided) or asymmetric (more involved on one side) brain lesion (including arterial stroke, venous infarction, grade III or IV intraventricular haemorrhage [IVH] or periventricular leukomalacia [PVL]), that was confirmed from neonatal cranial ultrasound or neonatal MRI by a neonatologist; and lived within a 200-km radius of the Royal Brisbane and Women’s Hospital in Queensland, Australia (south-east Queensland cohort), or lived in Pisa, Modena and Genoa in Italy (Italian cohort). Infants with epileptic seizures who remained unstable on medications, and/or with hydrocephalus requiring a shunt, and/or with confirmed with retinopathy of prematurity stage III to stage V were excluded.

**Healthy infants**

Healthy infants were eligible for inclusion if they: were between 38 and 41 weeks gestational age (GA) or between 0 and 9 weeks post-term age at time of enrollment; had an uncomplicated delivery and lived within a 200-km radius of the Royal Brisbane and Women’s Hospital in Queensland, Australia (south-east Queensland cohort). Infants who were born preterm with/without post-natal complications were excluded.

**Enrolled infants**

At this young age, it was not possible to determine which type of UL impairment was likely to develop. Therefore, once enrolled, infants with asymBI were considered to have a potentially impaired and potentially unimpaired UL (as well as the lower limbs), based on the side of the brain (for unilateral brain lesions) or the more involved side of the brain (for asymmetric brain lesions) where the lesion was located.
All infants with asymBI and all healthy infants, as participants of the UP-BEAT Study, were receiving intervention. Infants in each group were randomly allocated to receive Action Observation Training (AOT; intervention) or Toy Observation Training (TOT; sham control). There were equal numbers of participants in the AOT and TOT groups.

3.5. Sample size calculations

Sample size of the parallel RCT sample for each cohort (i.e. healthy and asymBI) was based on the larger ARC-funded RCT, on the assumption that the effect size (ES) of the proposed training in the RCT would be similar to that found in a previously published randomised clinical trial. This trial examined a comparable UL movement training program, with a mean effect size of 2.4, which was measured on the variables of hand-toy contact and hand-toy contact duration, after eight weeks of UL movement training. Given the high ES, the calculation returned a sample of only four participants per group, on a two-tailed t-test, significance (alpha) level of 0.05 and 80% power. The sample population of this clinical trial comprised full-term and preterm infants (n=26; 13 preterm, 13 full-term), the latter at risk of CP.

Similarly, the sample population of this doctoral program comprised healthy, term-born infants and infants with asymBI, who were at high risk of UCP (including preterm infants). Our population was predicted to involve two sub-groups of lesion type (i.e. arterial stroke and venous infarction) and would be highly variable with the presence of unilateral or asymmetric brain injury. The sample was therefore quadrupled, which resulted in an intended total sample of 32 infants. There were 47 healthy infants and 33 infants with asymBI enrolled in the parallel RCTs (total RCT sample of 80 infants). The parallel RCTs were adequately powered, with 89% retention for healthy infants and 82% retention of infants with asymBI at the six month follow-up assessment.

The COSMIN guidelines provided guidance an adequate sample sizes required for evaluation of internal consistency and reliability of the GRAB. For evaluation of internal consistency and reliability, the COSMIN guidelines suggest that: (i) an ‘excellent’ sample size is ≥ 100; (ii) a ‘good’ sample size is 50-99); (iii) a ‘fair’ sample size is 30-49; and (iv) a ‘poor’ sample size is < 30. There was no available evidence to provide guidance for an adequate sample size for evaluation of construct validity and predictive validity of the GRAB.
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with recruitment for the parallel RCT sample for both cohorts (particularly the asymBI cohort); and study drop outs prior to and following the six month follow-up assessment. This resulted in smaller samples being included in each of the studies on the GRAB. Refer to Figure 3.1. for a flowchart of infants included from referral to the parallel RCTs; and the sample sizes used for validity, reproducibility and longitudinal testing of the GRAB.

The sample sizes were relatively small for each study, however, there were significant amounts of data analysed. All available toy presentations were analysed in clusters of six (to represent the total possible six toy presentations for each infant) for each infant, for each assessment occasion; and each UL was scored separately for each infant, for each assessment occasion. The design effect (Deff) was calculated for evaluation of internal consistency and reproducibility of the GRAB, which is the amount that a sample size needs to be multiplied in a study that involves cluster sampling. Calculation of the Deff is based on the intraclass correlation coefficient (ICC) and the average cluster size. The ICC represents the ratio of the between-cluster variance to the total variance of the sample. An equivalent sample size that reflects the amount of data that is contributed by each infant can then be calculated, based on the total number of toy presentations and the Deff. Calculations of the Deff and equivalent sample sizes for each study on the GRAB are presented in Table 3.1.

Validity study

There was no available evidence to provide guidance for an adequate sample size for evaluation of construct validity of the GRAB. The sample size for the construct validity analysis at 18 weeks C.A. was 44 infants; and 496 toy presentations were analysed (six infants had less than six toy presentations due to a faulty video camera or infants becoming irritable and/or fatigued during the assessment).

As the evaluation of internal consistency involved analysing clusters of toy presentations (whereby one cluster contains a total possible six toy presentations) for each infant and for each assessment occasion, the design effect (Deff) was calculated using the following formula: Deff = 1 + (n’ – 1) x ICC; whereby Deff refers to the design effect, n’ refers to the average cluster size, and ICC refers to the intraclass correlation coefficient. The equivalent sample sizes for each behavioural event (i.e. number of unimanual contacts, unimanual grasps and bimanual grasps)
for the internal consistency analysis were calculated using the following formula: total number of toy presentations / Deff. There were 180 toy presentations analysed in total. Refer to Table 3.1. for calculations of the Deff and equivalent sample size for each behavioural event. Based on the total of 180 toy presentations for n=15 infants, the equivalent sample size for evaluation of internal consistency of the GRAB ranged from 51 to 75 infants. This equivalent sample size represents a ‘good’ sample size according to the COSMIN guidelines. There was variability demonstrated by infants across behavioural events (i.e. ICC values ranging from 0.28 to 0.51).

Reproducibility study

As the evaluation of reproducibility (i.e. reliability and agreement) involved analysing clusters of six total possible toy presentations (similarly to evaluation of internal consistency above) for each infant and for each assessment occasion, the Deff and the equivalent sample size were calculated for each behavioural event. There were 180 toy presentations analysed in total.
Figure 3.1. Number of infants included in the parallel randomised controlled trials for the UP-BEAT Study; and sample sizes for the validity, reproducibility and longitudinal studies on the Grasp and Reach Assessment of Brisbane.
Refer to Table 3.1. for calculations of the Deff and equivalent sample size for each behavioural event. Based on the total of 180 toy presentations for n=13 infants, the equivalent sample size for evaluation of internal consistency of the GRAB ranged from 52 to 68 infants. This equivalent sample size represents a 'good' sample size according to the COSMIN guidelines. There was variability demonstrated by infants across behavioural events (i.e. ICC values ranging from 0.23 to 0.50).

**Longitudinal study**

There was no available evidence to provide guidance for an adequate sample size for evaluation of predictive validity of the GRAB. The sample size for the longitudinal analysis of the GRAB (which involved predictive validity) at 14, 16 and 18 weeks C.A. was 41/52 infants (11 infants had missed appointments; three at 14 weeks C.A., six at 16 weeks C.A. and two at 18 weeks C.A.). There were 1436 toy presentations analysed (six infants had less than six toy presentations due to a faulty video camera or infants becoming irritable and/or fatigued during the assessment).

At the time of writing the first draft of the longitudinal paper, several infants with asymBI had not yet completed their six and 12 month follow up assessments on the BSID III. There were 26 out of 32 infants with asymBI who were available to return for their six month follow-up assessment (two drop outs and four who were not yet six months C.A.). There were 18 out of 32 infants with asymBI who were available to return for their 12 month follow-up assessment (six drop outs and eight who were not yet 12 months C.A.). The analysis will therefore be updated and this paper will be submitted after data collection is completed in December 2015.

**3.6. Measures and procedures**

The primary outcome of this doctoral program was quantity of unimanual and bimanual reach and grasp behaviours at 14, 16 and 18 weeks C.A., measured on the GRAB. The secondary outcome of this doctoral program was FM development at six and 12 months C.A., measured on the BSID III. Aim 4 of this doctoral program was addressed by measuring unimanual and bimanual reach and grasp on the GRAB, as well as FM development on the BSID III.
3.6.1. The Grasp and Reach Assessment of Brisbane (GRAB)

The GRAB was initially called the ‘Reaching and Grasping Assessment’ (as reported in the UP-BEAT Study protocol, Appendix 9.2.) and was developed by the research team as a quantitative measure to: (i) detect asymmetries between ULs in early reach and grasp behaviours in infants with asymBI; and (ii) identify differences in reach and grasp behaviours between healthy, term-born infants and infants with asymBI.

Rationale for chosen time points on the GRAB

The GRAB was designed to measure behaviours that are involved in early UL motor development prior to six months of age, namely unimanual and bimanual reaching and grasping. Typically developing infants in Western cultures have been observed to acquire the important motor skills of reaching between three to five months of age\(^{30,32,157}\) and grasping as early as 18 weeks.\(^{21}\) Prior to reach onset, which has been reported to occur around four months of age, (i.e. 16 weeks\(^{157,158}\)) infants have been observed to demonstrate prehensile movements. These movements provide infants with multimodal input about their UL function within their environment, and provide sensorimotor experiences that can help infants learn how to control their ULs.\(^{23,25}\)

Brief description of the structured play session of the GRAB

Infants were assessed at home, during the morning when they were in a calm and alert state. Infants were seated in a Baby Björn Babysitter Balance® infant chair and presented with three (out of four) toys in the midline, in a block design consisting of six 30-second trials of toy presentation, separated by five 30-second trials of no toy presentation (total toy presentation time of three minutes within 5.5 minutes of video time). The toys were similar in material, shape, size and appearance, differing only in colour combination. Colour combinations were coded based on the colour of the body and head of the toy and were yellow/red, pink/orange, red/green, and green/red. The task was filmed with a video camera (approximately 1.2 metres above the infant) which captured a full view of infants, their ULs and the toys. A more detailed description of the development of the GRAB (including the structured play session) is provided in Chapter 4. Refer to Figure 3.2. for a photograph of the toys utilised in the GRAB; and Figure 3.3. for a schematic drawing of the GRAB set-up.
Development of the GRAB scoring criteria and procedures

Video recordings of the GRAB were edited into six separate video-clips for each toy presentation (one edited video-clip=700 frames) using QuickTime Pro™ v.7.6.9. These edited video-clips were then scored by one independent rater who was masked to developmental status. The development of the scoring criteria and method of the GRAB involved an iterative process that consisted of six stages, and are summarised in Table 3.2. Each stage of development prior to finalising the scoring method and criteria of the GRAB (stages one to five) are described in detail and included as Appendix 9.3.

The variables measured on the GRAB were originally: (i) frequency of hand-toy contacts as a duration of time (in frames out of a total possible 700 frames per video-clip); and (ii) orientation of the hand during toy contact (i.e. ‘palmar’ or ‘dorsal’). Variables were recorded using a hard-copy scoring sheet. The final revision of the scoring method of the GRAB involved using the free annotation software ELAN and exporting the data into a Microsoft Excel spreadsheet to measure and record seven unimanual reach and grasp behaviours and two bimanual reach and grasp behaviours (outlined in ‘Final version of the GRAB scoring criteria’).

Key factors that necessitated revisions in the criteria and scoring method of the GRAB were: (i) analysis of each UL separately to examine differences in unimanual behaviour between ULs; (ii) consideration of hand orientation during unimanual toy contact as a potential indicator of differences between infants with asymBI and healthy infants; (iii) consideration of visual attention as a potential influence on unimanual behaviour; (iv) analysis of both ULs together to examine differences in bimanual behaviour between infants with asymBI and healthy infants; (v) analysis of several unimanual and bimanual UL behaviours ranging from small to large quantities depending on individual maturation of reach to grasp development over a relatively short period of video time; (vi) amount of time required to score and analyse video-recordings; (vii) difficulties or issues encountered with event differentiation and hand orientation following pilot scoring of video-recordings; (viii) discussion of the most suitable method to measure, record, analyse and present the data; and (ix) reaching consensus in the research team for definitions of each behaviour.
Table 3.1. Calculations of the design effect and equivalent sample sizes for internal consistency and reproducibility of the Grasp and Reach Assessment of Brisbane.

<table>
<thead>
<tr>
<th>Behavioural event on the GRAB</th>
<th>Internal consistency (validity paper)</th>
<th>Reliability/agreement (reproducibility paper)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Calculation of the Deff:</td>
<td>Calculation of the equivalent sample size:</td>
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<tr>
<td></td>
<td>( Deff = 1 + (n' - 1) \times ICC )</td>
<td>( Total\ number\ of\ toy\ presentations / Deff )</td>
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<tr>
<td>Number of unimanual contacts</td>
<td>Deff = 1 + (6 - 1) \times 0.51</td>
<td>Deff = 1 + (6 - 1) \times 0.50</td>
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<td></td>
<td>Deff = 1 + (5 \times 0.51)</td>
<td>Deff = 1 + (5 \times 0.50)</td>
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<tr>
<td></td>
<td>Deff = 1 + 2.55</td>
<td>Deff = 1 + 2.5</td>
</tr>
<tr>
<td></td>
<td>Deff = 3.55</td>
<td>Deff = 3.5</td>
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<tr>
<td></td>
<td>180 / 3.55 = 51 infants</td>
<td>180 / 3.5 = 52 infants</td>
</tr>
<tr>
<td>Number of unimanual grasps</td>
<td>Deff = 1 + (6 - 1) \times 0.28</td>
<td>Deff = 1 + (6 - 1) \times 0.39</td>
</tr>
<tr>
<td></td>
<td>Deff = 1 + (5 \times 0.28)</td>
<td>Deff = 1 + (5 \times 0.39)</td>
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<tr>
<td></td>
<td>Deff = 1 + 1.4</td>
<td>Deff = 1 + 1.95</td>
</tr>
<tr>
<td></td>
<td>Deff = 2.4</td>
<td>Deff = 2.95</td>
</tr>
<tr>
<td></td>
<td>180 / 2.4 = 75 infants</td>
<td>180 / 2.95 = 61 infants</td>
</tr>
<tr>
<td>Number of bimanual grasps</td>
<td>Deff = 1 + (6 - 1) \times 0.33</td>
<td>Deff = 1 + (6 - 1) \times 0.33</td>
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<tr>
<td></td>
<td>Deff = 1 + (5 \times 0.33)</td>
<td>Deff = 1 + (5 \times 0.33)</td>
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<tr>
<td></td>
<td>Deff = 1 + 1.65</td>
<td>Deff = 1 + 1.65</td>
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<tr>
<td></td>
<td>Deff = 2.65</td>
<td>Deff = 2.65</td>
</tr>
<tr>
<td></td>
<td>180 / 2.65 = 68 infants</td>
<td>180 / 2.65 = 68 infants</td>
</tr>
</tbody>
</table>

Key. GRAB, Grasp and Reach Assessment of Brisbane; Deff, design effect.
Figure 3.2. Photograph of the toys presented to infants in the Grasp and Reach Assessment of Brisbane.

Figure 3.3. Schematic drawing of the set-up of the Grasp and Reach Assessment of Brisbane.

(a) Camera
(b) Toy presented on a stick
(c) Screen
(d) Slightly reclined infant chair (40°)
The final revision enabled the rater to utilise the GRAB to quantitatively measure, record and analyse the developmental progression of early unimanual and bimanual reach and grasp behaviours. Duration of scoring ranged from 30 minutes to one hour, depending on the quantity of behaviours demonstrated by each infant in each 30-second video-clip of a single toy presentation.

Final version of the GRAB scoring criteria

Behaviours observed from edited GRAB video-clips were scored using the free annotation software ELAN.\textsuperscript{160,161} Scores from each video-clip, for each infant, were then collated into a Microsoft Excel spreadsheet. Advantages of using the ELAN software compared to previously trialled software programs (see detailed descriptions in Appendix 3) included: (i) ability to annotate each outcome for each UL separately using a numerical code as well as brief notes as required, straight from the video-clips; (ii) an in-built feature that automatically converted the duration of each outcome from frames into seconds; and (iii) an in-built feature that exported the data into a simple format to analyse in Microsoft Excel.

Refer to Table 3.2. for a summary of recorded behaviours measured on the GRAB at each stage of development; and Table 3.3. for the final GRAB scoring criteria with definitions of each behaviour. The seven unimanual reach and grasp behaviours and two bimanual reach and grasp behaviours were further categorised into ‘behavioural events’ (i.e. behaviour quantified by a discrete number of counts) and ‘behavioural duration’ (i.e. length of time in seconds that a behaviour was observed). The unimanual and bimanual behavioural events were: (i) number of unimanual contacts; (ii) number of unimanual grasps; and (iii) number of bimanual midline grasps. Unimanual and bimanual behavioural duration were: (i) duration of no unimanual activity; (ii) duration of unimanual prehensile movements; (iii) duration of unimanual transport phase; (iv) duration of unimanual contribution to hands at midline; (v) duration of other unimanual activity; (vi) duration of bimanual midline grasps; and (vii) duration of bimanual midline behaviour. Duration of behaviours as a percentage of total toy presentation time were then calculated using a Microsoft Excel scoresheet. These behaviours were discussed by the research team to reflect early reach to grasp development in infants and would enable detection of asymmetries between ULs, as well as differences between infants with asymBI and healthy infants. It was predicted that infants with asymBI, compared to healthy infants, would demonstrate a paucity of: unimanual prehensile movements, transport
phase, contribution to hands at midline and bimanual midline grasps; and a significantly greater proportion of no unimanual activity and other activity.

To determine the presence of asymmetries between ULs on the GRAB, and to compare infants with asymBI to healthy infants; an asymmetry index (AI) was calculated for number of unimanual contacts and grasps. The AI was calculated as the absolute value (|) of the difference in contacts and grasps between ULs, divided by the total number of contacts and grasps for both ULs. For the asymBI group, \( AI = |(I - U)| / |(I + U)| \) (formula 1); whereby \( I \) refers to the impaired UL and \( U \) refers to the unimpaired limb. For the healthy group, \( AI = |(L - R)| / |(L + R)| \) (formula 2); whereby \( L \) refers to the left limb and \( R \) refers to the right UL. The range of AI was 0 to 1, with an AI of 0 indicating complete symmetry between ULs and an AI of 1 indicating complete asymmetry between ULs. The AI values for the number of unimanual contacts and grasps were then converted into a percentage (from 0 to 100%) to indicate the proportion of total toy presentation time that unimanual contacts and grasps were asymmetric between ULs for each group.

As discussed in 3.5. ‘Sample size calculations’, evaluation of internal consistency and reproducibility of measurements on the GRAB were performed by analysing 15 randomly selected assessment occasions from both healthy, term-born infants and infants with asymBI. The statistical analyses undertaken to evaluate internal consistency and reproducibility of the GRAB are presented briefly below in section 3.7. ‘Statistical Analyses’; and in detail in Chapters 4 and 5. The results of the analyses and discussion of the findings are presented in Chapters 4 and 5. Furthermore, in the longitudinal study on the GRAB (mentioned briefly in 3.5. ‘Sample calculations’), infants were also assessed at six and 12 months C.A. on the BSID III. Specifically, the BSID III Motor Scale was used to determine if longitudinal reach to grasp development on the GRAB would predict motor development at six and 12 months C.A.
### Table 3.2.
Recorded behaviours measured on the Grasp and Reach Assessment of Brisbane (GRAB) at each stage of development.

<table>
<thead>
<tr>
<th>Stage 1</th>
<th>Stage 2</th>
<th>Stage 3</th>
<th>Stage 4</th>
<th>Stage 5</th>
<th>Stage 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration (F) of toy contact</td>
<td>Duration (F) of toy contact</td>
<td>Unimanual Activity outcomes:</td>
<td>Duration (F) of toy contact</td>
<td>Detection of asymmetry</td>
<td>Unimanual outcomes:</td>
</tr>
<tr>
<td>‘Palmar’ toy contact or</td>
<td>‘Palmar’ toy contact or</td>
<td>Duration (F) of no toy contact</td>
<td>Duration (F) of ‘palmar’ toy contact</td>
<td>between hands:</td>
<td>Duration (S) of no unimanual activity</td>
</tr>
<tr>
<td>‘Dorsal’ toy contact</td>
<td>‘Dorsal’ toy contact</td>
<td>Duration (F) of ‘palmar open’ toy contact</td>
<td>Duration (F) of ‘palmar open’ toy contact</td>
<td></td>
<td>Duration (S) of prehensile movements</td>
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<tr>
<td>Duration of VA</td>
<td>Duration of no VA</td>
<td>Duration (F) of ‘palmar closed’ toy contact</td>
<td>Duration (F) of ‘palmar closed’ toy contact</td>
<td></td>
<td>Duration (S) of transport phase</td>
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<tr>
<td>Unimanual Interaction outcomes:</td>
<td>Duration (F) of ‘dorsal open’ toy contact</td>
<td>Duration (F) of VA</td>
<td>Duration (F) of VA with toy contact</td>
<td></td>
<td>Duration (S) of contribution to hands at midline</td>
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<tr>
<td>Duration (F) of no interaction</td>
<td>Duration (F) of ‘dorsal closed’ toy contact</td>
<td>Duration (F) of VA with toy contact without VA</td>
<td>Number of palmar contacts</td>
<td>Duration (S) of midline toy contacts</td>
<td>Number of contacts</td>
</tr>
<tr>
<td>Duration (F) of VA with toy contact</td>
<td>Number of dorsal open contacts</td>
<td>Additional unimanual activity outcomes:</td>
<td>Number of dorsal closed contacts</td>
<td>Duration (S) of midline toy contacts with VA</td>
<td>Number of grasps</td>
</tr>
<tr>
<td>Duration (F) of toy contact without VA</td>
<td>Number of dorsal closed contacts</td>
<td>Unimanual Activity outcomes:</td>
<td>Detection of asymmetry</td>
<td>Early reach to grasp</td>
<td>Bimanual outcomes:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Duration (F) of toy contact</td>
<td>between hands:</td>
<td>development for each hand:</td>
<td>Number of bimanual midline grasps</td>
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<tr>
<td></td>
<td></td>
<td>Duration (F) of toy contact without VA</td>
<td>Duration (F) of no interaction</td>
<td>Duration (S) of no activity (0)</td>
<td>Duration (S) of bimanual midline grasps</td>
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<td></td>
<td></td>
<td>Additional unimanual interaction outcomes:</td>
<td>Duration (F) of VA with toy contact</td>
<td>Duration (S) of prehensile movements</td>
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<tr>
<td></td>
<td></td>
<td>Number of palmar contacts</td>
<td>Number of dorsal open contacts</td>
<td>Duration (S) of transport phase</td>
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<td></td>
<td></td>
<td>Number of dorsal closed contacts</td>
<td>Number of dorsal closed contacts</td>
<td>Duration (S) of reach and toy contacts</td>
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<td></td>
<td>Additional unimanual interaction outcomes:</td>
<td>Additional unimanual interaction outcomes:</td>
<td>Duration (S) of toy grasps</td>
<td>Duration (S) of bimanual midline behaviour</td>
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<td></td>
<td></td>
<td>Duration (S) of no interaction</td>
<td>Duration (S) of no interaction</td>
<td>Duration (S) of toy manipulation</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Duration (S) of visual attention</td>
<td>Duration (S) of visual attention</td>
<td>Duration (S) of toy manipulation</td>
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<td></td>
<td></td>
<td>Duration (S) of VA with toy contact</td>
<td>Duration (S) of VA with toy contact</td>
<td>Duration (S) of other activity</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Duration (S) of toy contact without VA</td>
<td>Duration (S) of toy contact without VA</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Key.** VA, visual attention; F, frames; S, seconds.
### Table 3.3.
**Final scoring criteria of the Grasp and Reach Assessment of Brisbane (GRAB).**

<table>
<thead>
<tr>
<th>Upper limb behaviour</th>
<th>Definition of upper limb behaviour</th>
<th>Scoring code(^1*) (recorded using ELAN software)</th>
<th>Conversion into GRAB score using Microsoft Excel scoresheet(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No unimanual activity</td>
<td>No anticipatory movements towards the toy (e.g. no excitable motoric actions) and no attempts to approach the toy (e.g. no prehensile hand or finger movements). Hand/arm may be static.</td>
<td>0</td>
<td>Duration of no unimanual activity</td>
</tr>
<tr>
<td>Unimanual prehensile movements</td>
<td>Anticipatory movements towards the toy (e.g. excitable motoric actions) and/or preparatory movements in an attempt to approach the toy (e.g. prehensile hand or finger movements).</td>
<td>1</td>
<td>Duration of unimanual prehensile movements</td>
</tr>
<tr>
<td>Unimanual transport phase</td>
<td>Arm movements (e.g. swiping and reaching) towards the toy, in an attempt to contact the toy, without contacting the toy.</td>
<td>2</td>
<td>Duration of unimanual transport phase</td>
</tr>
<tr>
<td>Unimanual contribution to hands at midline</td>
<td>Each hand is at the midline. Hands may be touching or clasped together, without contacting the toy.</td>
<td>3</td>
<td>Duration of unimanual contribution to hands at midline</td>
</tr>
<tr>
<td>Unimanual contact</td>
<td>Any contact initiated by the infant with any part of the toy (i.e. head, body, arms, hands, stick). If the assessor uses the toy to contact the infant’s hand or arm to capture attention, for instance, this is not considered a toy contact.</td>
<td>4</td>
<td>Number of unimanual contacts and duration of unimanual contacts</td>
</tr>
</tbody>
</table>

*Examples of toy contact:*
- Infant’s hand is open, fingers are extended or flexed, and the surface of the hand makes contact with the toy;
- Infant’s hand is loosely closed with fingers flexed around the toy, and the surface of

---

\(^1\)The scoring code of 0-6 was used to analyse each upper limb behaviour demonstrated by infants for each video-recorded toy presentation. For each assessment occasion, three toys were presented in a random order, with a total of six toy presentations. The total possible duration of toy presentation for each assessment occasion was three minutes out of a total video-recorded duration of 5.5 minutes.

\(^2\)Each scored behaviour that was recorded using the ELAN software was imported into a scoresheet using Microsoft Excel, whereby scores were converted into duration of time (seconds) to reflect the duration of time that a unimanual or bimanual behaviour was observed for each toy presentation. The total frequency of unimanual contacts and grasps was calculated by counting the total number of occurrences recorded for each ELAN score of 4 and 5, across the six toy presentations. The total duration of unimanual behaviours (no activity, prehensile movements, transport phase, contribution to hands at midline, contacts, grasps, and other activity) was calculated by adding up the duration of each ELAN score of 0-6, across the six toy presentations. The total frequency of bimanual midline grasps was calculated by counting the total number of occurrences recorded for each ELAN score of 5 that involved both ULs simultaneously grasping for any duration. The total duration of bimanual behaviours (midline grasps and midline behaviour) was calculated by adding up the duration of each ELAN score of 3 (which involved both ULs simultaneously at the midline for any duration) and 5 (which involved both ULs simultaneously grasping for any duration).
the hand makes contact with the toy;  
*Infant's hand is fisted with fingers tightly flexed, and the surface of the hand makes contact with the toy.*

**Unimanual grasp**  
Grasping the toy using all or most fingers with the palm, and closing around the toy. Grasping may be brief or the toy may be held for a prolonged period of time. The infant may also adjust his/her grasp around the toy; and/or manipulate the toy with finer movements around the toy's head/arms/hands.

**Number of unimanual grasps and duration of unimanual grasps**  
5

**Other unimanual activity**  
An alternative arm/hand activity that is not directed towards the toy (e.g. hand out to side of torso, hand to mouth, contacting or grasping clothing).

**Duration of other unimanual activity**  
6

**Bimanual midline grasp**  
Grasping the toy with both hands simultaneously in the midline.

**Number of bimanual midline grasps and duration of bimanual midline grasps**  
N/A – scored as unimanual grasp by both hands simultaneously.

**Bimanual midline behaviour**  
Both hands are at the midline. Hands may be touching or clasped together, without contacting the toy.

**Duration of bimanual midline behaviour**  
N/A – scored as unimanual contribution to hands at midline by both hands simultaneously.

**Key.** GRAB, Grasp and Reach Assessment of Brisbane; N/A, not applicable. *.
3.6.2. The Bayley Scales of Infant and Toddler Development (BSID III)

The BSID III was used in this doctoral program primarily to measure FM development in both healthy infants and infants with asymBI; and to examine its relationship with longitudinal reach and grasp development, measured on the GRAB. As outlined in Hypothesis 4 of this doctoral program, it was anticipated that: (i) differences in the longitudinal development of reach and grasp behaviours between groups at 14, 16 and 18 weeks C.A. on the GRAB; and (ii) differences between ULs in the asymBI group at 14, 16 and 18 weeks C.A. on the GRAB would predict delayed FM development at six and 12 months C.A. on the BSID III FM subtest in the asymBI group compared to the healthy group. In addition, the potential influences of other developmental factors such as GM and cognitive ability were considered by measuring GM and cognitive development (BSID III GM subtest and Cognitive composite scale, respectively).

The BSID III is a norm-referenced, standardized developmental assessment used to detect developmental delay in infants and young children from one to 42 months of age. The BSID III consists of a series of simple interactions with the infant and the total administration time ranges from approximately 50 to 80 minutes. This measure aims to: (i) provide a developmental profile to compare the strengths and limitations of an individual to a normal population; and (ii) identify children who may require intervention and access to support services. Its clinical utility in various populations of children, however, has not yet been established. This assessment was performed at six and 12 months C.A.

Rationale for chosen time points on the BSID III

These time points were chosen as: reaching and grasping are expected to be established by six months of age; bimanual manipulation is expected to be established by 12 months of age; and the BSID III incorporates these behaviours in the FM subtest at these time points.

Validity and reliability of the BSID III

A summary of validity and reliability of the BSID III is presented in Table 3.3. Moderate concurrent validity has been reported between the earlier and current versions of the BSID; and between the BSID III and the Peabody Developmental Scales (second edition, PDMS-2). Moderate to strong concurrent validity has been reported between the BSID III and the Wechsler Preschool and Primary Scale
of Intelligence (third edition, WPPSI III). The BSID III has also demonstrated strong internal consistency at six and 12 months; and strong test-retest reliability between nine to 13 months. Test-retest reliability at six months on the BSID III has not been reported.

Scoring of the BSID III

Each test item was given a score of 0 (did not perform task) or 1 (did perform task) throughout the assessment, which continued until the infant reached a ceiling score of 0 for 5 consecutive items. Following the assessment, the assessor calculated total raw scores for the Cognitive composite scale, the FM subtest and the GM subtest. Using the data provided in the administration manual, total raw scores were converted into scaled scores, and the sum scaled scores were converted into a composite score with a percentile rank and a confidence interval.

3.7. Statistical analysis

3.7.1. Validity study to address Aim 2

To evaluate construct validity and internal consistency of the GRAB, a validity study was undertaken. It was predicted that the GRAB would demonstrate evidence of strong construct validity and internal consistency as a quantitative measure for: (i) detecting asymmetries between ULs in reach and grasp behaviours in infants with asymBI; and (ii) identifying differences in reach and grasp behaviours between healthy infants and infants with asymBI.

Characteristics of infants with asymBI were compared with those of healthy infants aged 18 weeks C.A., using an independent samples t-test for GA and a Fisher’s Exact Test for gender, side and type of brain lesion. The internal consistency for time phase and toy colour phase was determined by calculating Cronbach’s alpha coefficients. A Cronbach’s alpha coefficient value of 0.70 is considered acceptable, while values above 0.80 are preferable.

The association between UL (i.e. left and right for healthy group; potentially impaired and unimpaired for asymBI group) and number of unimanual contacts/grasps and each was investigated using mixed effects Poisson regression. Main effects included in the model were group (i.e. healthy/asymBI) and UL, and a group by UL interaction term was also included. Infant ID was included as a random effect to account for possible non-independence of outcomes within each infant.
Table 3.3. Summary of validity and reliability of the Bayley Scales of Infant and Toddler Development (BSID III).

<table>
<thead>
<tr>
<th>BSID III scale or subtest</th>
<th>Scale or component of measure for comparison</th>
<th>Strength of correlation (r)</th>
<th>Interpretation</th>
<th>Study sample</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Concurrent validity (BSID III vs BSID II)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Motor composite scale</td>
<td>BSID II Motor Index</td>
<td>0.60</td>
<td>Moderate</td>
<td>Healthy infants and children (n=108) of different ethnic origins (i.e. Caucasian, African American, Hispanic) aged 1 to 42 months</td>
</tr>
<tr>
<td>FM subtest</td>
<td>BSID II Motor Index</td>
<td>0.52</td>
<td>Moderate</td>
<td>Same as above</td>
</tr>
<tr>
<td>GM subtest</td>
<td>BSID II Motor Index</td>
<td>0.54</td>
<td>Moderate</td>
<td>Same as above</td>
</tr>
<tr>
<td>Cognitive composite scale</td>
<td>BSID II Mental Index</td>
<td>0.60</td>
<td>Moderate</td>
<td>Same as above</td>
</tr>
<tr>
<td><strong>Concurrent validity (BSID III vs PDMS-2)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Motor composite scale</td>
<td>Total Motor Quotient</td>
<td>0.57</td>
<td>Moderate</td>
<td>Healthy infants and children (n=81) of different ethnic origins (i.e. Caucasian, African American, Hispanic) aged 2 to 42 months</td>
</tr>
<tr>
<td>FM subtest</td>
<td>FM Quotient</td>
<td>0.59</td>
<td>Moderate</td>
<td>Same as above</td>
</tr>
<tr>
<td>GM subtest</td>
<td>GM Quotient</td>
<td>0.59</td>
<td>Moderate</td>
<td>Same as above</td>
</tr>
<tr>
<td><strong>Concurrent validity (BSID III vs WPPSI III)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Motor composite scale</td>
<td>VIQ</td>
<td>0.52</td>
<td>Moderate</td>
<td>Healthy infants and children (n=57) of different ethnic origins (i.e. Caucasian, African American, Hispanic) aged 28 to 42 months</td>
</tr>
<tr>
<td>PIQ</td>
<td>0.52</td>
<td>Moderate</td>
<td>Same as above</td>
<td></td>
</tr>
<tr>
<td>FSIQ</td>
<td>0.55</td>
<td>Moderate</td>
<td>Same as above</td>
<td></td>
</tr>
<tr>
<td>FM subtest</td>
<td>VIQ</td>
<td>0.45</td>
<td>Moderate</td>
<td>Same as above</td>
</tr>
<tr>
<td>PIQ</td>
<td>0.44</td>
<td>Moderate</td>
<td>Same as above</td>
<td></td>
</tr>
<tr>
<td>FSIQ</td>
<td>0.47</td>
<td>Moderate</td>
<td>Same as above</td>
<td></td>
</tr>
<tr>
<td>GM subtest</td>
<td>VIQ</td>
<td>0.50</td>
<td>Moderate</td>
<td>Same as above</td>
</tr>
<tr>
<td>PIQ</td>
<td>0.52</td>
<td>Moderate</td>
<td>Same as above</td>
<td></td>
</tr>
<tr>
<td>FSIQ</td>
<td>0.54</td>
<td>Moderate</td>
<td>Same as above</td>
<td></td>
</tr>
<tr>
<td>Cognitive composite scale</td>
<td>VIQ</td>
<td>0.79</td>
<td>Strong</td>
<td>Same as above</td>
</tr>
<tr>
<td>PIQ</td>
<td>0.72</td>
<td>Strong</td>
<td>Same as above</td>
<td></td>
</tr>
<tr>
<td>FSIQ</td>
<td>0.79</td>
<td>Strong</td>
<td>Same as above</td>
<td></td>
</tr>
<tr>
<td>**BSID III scale or subtest group 1 (healthy)</td>
<td>BSID III scale or subtest group 2 (CP)</td>
<td>Effect size (ES)</td>
<td>Interpretation</td>
<td>Study sample</td>
</tr>
<tr>
<td>Predictive validity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FM subtest</td>
<td>FM subtest</td>
<td>1.8</td>
<td>Children with CP scored significantly lower than healthy children</td>
<td>Healthy children (n=1300) and children with CP (n=73) aged 5 to 42 months</td>
</tr>
<tr>
<td>GM subtest</td>
<td>GM subtest</td>
<td>2.9</td>
<td></td>
<td>Same as above</td>
</tr>
<tr>
<td>Cognitive composite scale</td>
<td>Cognitive composite scale</td>
<td>1.6</td>
<td></td>
<td>Same as above</td>
</tr>
</tbody>
</table>
### Table 3.3. (continued)
Summary of validity and reliability of the Bayley Scales of Infant and Toddler Development (BSID III).

<table>
<thead>
<tr>
<th>BSID III scale or subtest</th>
<th>Strength of correlation ((r)) at assessment 1 (6 mths)</th>
<th>Strength of correlation ((r)) at assessment 2 (12 mths)</th>
<th>Interpretation</th>
<th>Study sample</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Internal consistency</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Motor composite scale</td>
<td>0.90</td>
<td>0.88</td>
<td>Strong</td>
<td>Healthy infants and children (n=100 for each age group) of different ethnic origins (i.e. Caucasian, African American, Hispanic) aged 1 to 42 months</td>
</tr>
<tr>
<td>FM subtest</td>
<td>0.82</td>
<td>0.79</td>
<td>Strong</td>
<td>Same as above</td>
</tr>
<tr>
<td>GM subtest</td>
<td>0.89</td>
<td>0.92</td>
<td>Strong</td>
<td>Same as above</td>
</tr>
<tr>
<td>Cognitive composite scale</td>
<td>0.87</td>
<td>0.83</td>
<td>Strong</td>
<td>Same as above</td>
</tr>
<tr>
<td><strong>Test-retest reliability</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Motor composite scale</td>
<td>N/A</td>
<td>0.85</td>
<td>Strong</td>
<td>Healthy infants and children (n=197) of different ethnic origins (i.e. Caucasian, African American, Hispanic) aged 2 to 42 months (n=50/197 for age group 9-13 months)</td>
</tr>
<tr>
<td>FM subtest</td>
<td>N/A</td>
<td>0.86</td>
<td>Strong</td>
<td>Same as above</td>
</tr>
<tr>
<td>GM subtest</td>
<td>N/A</td>
<td>0.86</td>
<td>Strong</td>
<td>Same as above</td>
</tr>
<tr>
<td>Cognitive composite scale</td>
<td>N/A</td>
<td>0.77</td>
<td>Strong</td>
<td>Same as above</td>
</tr>
</tbody>
</table>

**Key.** BSID III, bayley scales of infant and toddler development (version three); BSID II, bayley scales of infant and toddler development (version two); FM, fine motor; GM, gross motor; PDMS-2, peabody developmental motor scales (second edition); WPPSI III, wechsler preschool and primary scale of intelligence (third edition); VIQ, verbal intelligence quotient composite scale; PIQ, performance intelligence quotient composite scale; FSIQ, full scale intelligence quotient composite scale; CP, cerebral palsy; mths, months; N/A, not available as this analysis was not reported.

**References.** 48, 163
The association between group and number of bimanual midline grasps was investigated using Poisson regression. The healthy group was defined to be the reference group. Specifically, the potentially impaired UL from the asymBI group was compared to the left UL from the healthy group (as the latter was expected to be the non-dominant hand); and the potentially unimpaired UL from the asymBI group was compared to the right UL from the healthy group (as the latter was expected to be the dominant hand). For within-group analyses, the right UL was used as the reference UL for the healthy group; and the unimpaired UL was used as the reference UL for the asymBI group. Where differences in duration of total toy presentations occurred (i.e. less than 180 seconds was captured), the logarithm of the actual duration of toy presentations was included as an offset in the Poisson model. Effect estimates calculated using Poisson models are reported as incidence rate ratios (IRR) with 95% confidence intervals (95% CIs).

Linear regression was used to investigate the association between group and AI for the number of unimanual contacts/grasps. The association between UL and the proportion of unimanual behaviours out of total toy presentation time (i.e. no activity, prehensile movements, transport phase, contribution to hands at midline, contacts, grasps and other activity) were investigated using a mixed effects linear regression. The association between group and the proportion of bimanual midline grasps/unimanual contribution to hands at midline out of total toy presentation time were investigated using a mixed effects linear regression, with infant ID included as a random effect. Effect estimates are reported as mean differences (MD). For all analyses a $p$-value < 0.05 was considered statistically significant. Analyses were conducted using Stata v.13.1.166

3.7.2. Reproducibility study to address Aim 3

To evaluate intra-rater and inter-rater reliability and agreement of measurements on the GRAB, a reproducibility study was undertaken. It was predicted that the GRAB would demonstrate evidence of strong intra- and inter-rater reliability and high percentage intra- and inter-rater agreement of measurements.

Characteristics of infants with asymBI were compared with those of healthy infants, using an independent samples t-test for GA and a Fisher’s Exact Test for gender, side and type of brain lesion. Intra-rater and inter-rater reliability were determined using a two-way analysis of variance (ANOVA) to calculate intraclass
correlation coefficients (ICC) for GRAB scores, derived from a mixed model.\textsuperscript{167,168} The ICC(3,1) model was selected as raters were not sampled.\textsuperscript{167,168} The ICC ranges from 0 to 1, whereby 1 indicates perfect consistency between scores.\textsuperscript{167} The strength of correlation between scores was evaluated using the following criteria: ICC > 0.90 indicates very strong correlation; 0.75-0.90 indicates strong correlation; and < 0.75 indicates weak to moderate correlation.\textsuperscript{169} Intra-rater and inter-rater agreement were determined using Bland Altman methods, which involved calculation of the mean difference between ratings, standard deviation of the differences, and the 95% limits of agreement.\textsuperscript{170,171} For all analyses, a $p$-value < 0.05 was considered statistically significant. All analyses were conducted using Stata v.13.\textsuperscript{166} Graphpad Prism™ was used to produce the Bland Altman plots.

\textbf{3.7.3. Longitudinal study to address Aim 4}

A longitudinal study was undertaken to examine development of reach to grasp from 14 to 18 weeks C.A. on the GRAB. The relationship between reach to grasp development from 14 to 18 weeks C.A. on the GRAB and FM development at six and 12 months on the BSID III FM subtest was examined. It was predicted that differences in the development of reach to grasp from 14 to 18 weeks C.A. between groups (healthy vs asymBI), as well as differences between ULs from 14 to 18 weeks C.A. in the asymBI group would predict delayed FM development at six and 12 months C.A. on the BSID III in infants with asymBI compared to healthy infants.

Characteristics of infants with asymBI were compared with those of healthy infants using an independent samples t-test for GA and actual age at assessment; and a Fisher’s Exact Test for gender, side and type of brain lesion, and parental cultural background. The frequency of unimanual and bimanual reach to grasp on the GRAB was determined by calculating the mean number of unimanual contacts/grasps and bimanual grasps at each time point (14, 16 and 18 weeks C.A.), in each group.

The association between UL (i.e. left and right for the healthy group; potentially impaired and unimpaired for the asymBI group) and number of unimanual contacts/grasps/bimanual grasps over time was investigated using mixed effects Poisson regression. Main effects included in the model were group (i.e. healthy/asymBI) and UL, and a group by UL interaction term was also included. Infant ID was included as a random effect to account for possible non-independence.
of outcomes within each infant. The association between group and number of unimanual contacts/grasps/bimanual grasps over time was investigated using Poisson regression. For between-group analyses, the asymBI group was defined to be the reference group. For within-group analyses, the potentially unimpaired UL was compared to the potentially impaired UL in the asymBI group; and the right UL was compared to the left UL in the healthy group. Effect estimates calculated using Poisson models are reported as incident rate ratios (IRRs) with 95% confidence intervals (95% CIs).

The associations between group (i.e. healthy/asymBI) and FM and GM raw/scaled/motor composite scores at and between six and 12 months C.A. on the BSID III Motor Scale were investigated using linear regression. The association between number of unimanual contacts/grasps/bimanual grasps at 18 weeks C.A., and all Motor Scale scores at six and 12 months C.A. for each group were investigated using linear regression. Effect estimates are reported as mean differences (MDs) or regression coefficients ($r$) with 95% CIs. For all analyses, a $p$-value < 0.05 was considered statistically significant. Analyses were performed using Stata v.13.1.166

3.8. Summary and conclusions

Chapter 3 described the design and methods of the doctoral program, which was a component of the larger UP-BEAT Study. The primary focus of the doctoral program was to report the development of the GRAB and undertake validation and reproducibility testing of the GRAB as a new quantitative measure to: (i) detect, quantify and evaluate asymmetries between ULs during early unimanual and bimanual reach and grasp behaviours at 14, 16 and 18 weeks C.A. in infants with asymBI; (ii) identify differences in early unimanual and bimanual reach and grasp behaviours between healthy infants and infants with asymBI at 14, 16 and 18 weeks C.A.; and (iii) examine longitudinal development of reach to grasp in relation to prediction of delayed FM development in infants with asymBI compared to healthy infants six and 12 months C.A. on the BSID III. The next chapter addresses Aim 2 by presenting paper 3, a measurement paper that reports the development, construct validity and internal consistency of the GRAB.
Chapter 4: Development and validation of the Grasp and Reach Assessment of Brisbane (GRAB)

4.1. Introduction

This chapter addresses Aim 2 in the paper, ‘Development, construct validity and internal consistency of the Grasp and Reach Assessment of Brisbane (GRAB)’. This validity study evaluates the construct validity and internal consistency of the GRAB. This paper initially describes the process undertaken to develop the GRAB, followed by evaluation of construct validity and internal consistency. It was predicted that the GRAB would demonstrate evidence of strong construct validity and internal consistency as a quantitative measure for: (i) detecting asymmetries between ULs in reach and grasp behaviours in infants with asymBI; and (ii) identifying differences in reach and grasp behaviours between healthy infants and infants with asymBI. It was also hypothesised that a ‘warm-up effect’ may be observed over time on the GRAB.

4.2. Paper 3: Development, construct validity and internal consistency of the Grasp and Reach Assessment of Brisbane (GRAB)

This paper was submitted to Infant Behavior and Development on 14th November, 2015, and is currently under review.

Title
Development, construct validity and internal consistency of the Grasp and Reach Assessment of Brisbane (GRAB) for infants with asymmetric brain injury

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Key words
infant, upper extremity function, asymmetric brain injury, unilateral cerebral palsy, assessment, construct validity, internal consistency
Competing Interests
The authors declare they have no competing interests.

Authors’ Contributions
RNB is the Australian Research Council (ARC) Chief Investigator A and AG is the partner investigator on the study. RNB, AG and JZ were responsible for writing and obtaining the major study grant from the ARC. AG defined the original assessment protocol, and together with RNB, led the modification of the assessment protocol to the present design. RNB, AG, JZ and MP are responsible for all ethics applications and ethical reporting of the study outcomes. AG, VB, GT and MP led the modification of the assessment scoring protocol. MP scored all assessment occasions for the internal consistency analysis. RSW provided guidance and assistance on statistical analysis. All authors have read and approved the final manuscript.

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4.2.1. Abstract

Introduction

Infants with asymmetric brain injury (asymBI) are at high risk of unilateral Cerebral Palsy (UCP). The Grasp and Reach Assessment of Brisbane (GRAB) was developed to detect asymmetries in unimanual/bimanual upper limb (UL) reach and grasp behaviours in infants with asymBI. This study reports the development of the GRAB and evaluates its construct validity and internal consistency.

Material and methods

Prospective study of twenty four infants with asymBI and twenty healthy infants at 18 weeks corrected age (C.A.) in a structured play session. Three different coloured toys were presented at the midline in a block design of six 30-second trials of toy presentation, separated by five 30-second trials of no toy presentation. The number and duration of: (i) unimanual contacts; (ii) unimanual grasps; (iii) bimanual midline grasps; and (iv) duration of other unimanual behaviours (e.g. prehensile movements and transport phase) were measured. An Asymmetry Index (AI) was calculated to determine asymmetries between ULs. Possible AI values ranged from 0-100%, indicating proportion of toy presentation time that unimanual behaviours were asymmetric between ULs. Internal consistency of both the Time Phase (TP) and Toy Colour Phase (TCP) test items were determined by calculating Cronbach’s alpha coefficients. Each assessment occasion was split into six TPs and two TCPs; whereby one TP comprised one 30-second trial of one toy presentation and one TCP comprised two 30-second trials of the same toy presentation.

Results

For TP, seven out of nine unimanual behaviours and two out of three bimanual behaviours demonstrated strong internal consistency (Cronbach’s alpha coefficients 0.72-0.89). No unimanual activity demonstrated the strongest internal consistency (alpha=0.89). For TCP, six out of nine unimanual behaviours demonstrated strong internal consistency (alpha=0.73-0.82). Number of unimanual contacts and duration of unimanual prehensile movements demonstrated the strongest internal consistency (alpha=0.82). Duration of unimanual contribution to hands at midline and duration of bimanual midline behaviour demonstrated the weakest internal consistency for both TP and TCP (alpha=0.46-0.50). For unimanual contacts, the asymBI group were more asymmetric between ULs (mean AI=50%)
compared to the healthy group (mean AI=30%). For unimanual grasps, there were no differences between groups (both mean AI=40%). The healthy group were almost twice as likely to demonstrate bimanual grasps as the asymBI group (incidence rate ratio IRR 1.9, 95% CI 1.4 to 2.5, \( p < 0.001 \)). Infants with asymBI were less likely to use the impaired UL compared to the unimpaired UL for grasping (IRR 0.6, 95% CI 0.5 to 0.8, \( p < 0.001 \)); and used the impaired UL for a shorter proportion of time compared to the unimpaired UL for grasping (mean difference -9.1%, 95% CI -16.6 to -1.7, \( p=0.02 \)).

**Conclusions**

The GRAB is a research measure that detects and quantifies the presence or absence of unimanual and bimanual reach and grasp behaviours at 18 weeks C.A. in infants at risk of UCP. The GRAB demonstrated moderate to strong construct validity and strong IC within an assessment occasion. There was no toy preference or warm-up effect for TP or TCP for either group; confirming that the GRAB is a consistent measure across toy presentations within an assessment occasion. In this study, the GRAB identified that infants with asymBI demonstrated a paucity of unimanual and bimanual grasping compared to healthy, term-born infants; and demonstrated asymmetric unimanual grasping between ULs at 18 weeks C.A.
4.2.2. Introduction

Cerebral Palsy (CP\textsuperscript{3}) is the most common cause of motor impairment in young children (Surveillance of Cerebral Palsy in Europe),\textsuperscript{172} with a prevalence of approximately two to three in 1000 live births (Australian Cerebral Palsy Register).\textsuperscript{172,173} Unilateral CP (UCP) accounts for 18-36\% of children diagnosed with CP in Europe\textsuperscript{172} and 38\% of children diagnosed with CP in Australia.\textsuperscript{173} Infants with asymmetric brain injury (asymBI) are at high risk of developing UCP by the end of their first year of life.\textsuperscript{58} Unilateral impairment results in impaired development of reach and grasp, both of which are necessary for toy exploration. To date, the mini-Assisting Hand Assessment (mini-AHA) is the only validated measure to evaluate the use of the impaired upper limb (UL) during bimanual performance in infants with UCP aged eight to 18 months.\textsuperscript{12} There is no validated and published measure at present which evaluates asymmetries between ULs during early reach to grasp development in infants with asymBI who are younger than eight months C.A. Early detection of asymmetries between ULs is needed to provide an indication of an emerging hemiparesis in infants at risk of UCP.

At present, the average age in Australia for a diagnosis of CP is 19 months.\textsuperscript{174} Earlier detection of UCP is needed to enable timely referral to infant-friendly interventions within the critical period of brain development.\textsuperscript{58,60,175} Early detection of UCP involves identification of asymmetries in UL reaching (both spontaneous and purposeful), grasp ability and grasp strength.\textsuperscript{109} To date, UCP has been identified in infants with perinatal or neonatal stroke using: (i) asymmetries of wrist movements during the fidgety period (nine to 20 weeks post-term) of General Movements (GMs)\textsuperscript{176}; (ii) measurement of bimanual midline toy manipulation\textsuperscript{177}; and (iii) measurement of reaching trajectories.\textsuperscript{178}

More recently, very early detection of UCP in infants with asymBI (including perinatal or neonatal stroke) has been described, using two measures that are

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\textsuperscript{3}Abbreviations: ACPR, Australian Cerebral Palsy Register; AI, Asymmetry Index; asymBI, asymmetric brain injury; C.A., corrected age; CP, Cerebral Palsy; GA, gestational age; GMs, General Movements assessment; GRAB, Grasp and Reach Assessment of Brisbane; HAI, Hand assessment of Infants; IRR, incidence rate ratio; IVH, intraventricular haemorrhage; MD, mean difference; mini-AHA, mini-Assisting Hand Assessment; MRI, magnetic resonance imaging; N/A, not applicable; N/A, not calculated; PVL, periventricular leukomalacia; SCPE, Surveillance of Cerebral Palsy in Europe; SD, standard deviation; TP, time phase; TCP, toy colour phase; UCP, Unilateral Cerebral Palsy; UL, upper limb; 95\% CI, 95\% confidence interval.
currently under development: (i) the Hand Assessment of Infants (HAI)\(^{10}\); and (ii) the Grasp and Reach Assessment of Brisbane (GRAB).\(^ {10,110}\) The HAI was developed to evaluate asymmetries between ULs in goal-directed unimanual and bimanual UL actions in infants with asymBI aged three to 12 months.\(^ {10,151}\) The GRAB was developed to evaluate asymmetries between ULs in emerging reach and grasp behaviours in infants with asymBI aged 14 to 18 weeks C.A.\(^ {58}\)

This study is the first to report on the psychometric properties of the GRAB, and aims to: (i) describe its development; (ii) evaluate its construct validity; and (iii) determine its internal consistency. This study hypothesised that the GRAB would: (i) demonstrate strong construct validity and internal consistency; (ii) detect asymmetries between ULs in unimanual reach and grasp behaviours in infants with asymBI; and (iii) detect differences in unimanual/bimanual reach and grasp behaviours between healthy, term-born infants and infants with asymBI. It was also hypothesised that a ‘warm-up effect’ may be observed over time on the GRAB.

4.2.3. Materials and methods

Test item generation

A body of literature was examined to identify the theoretical basis of the GRAB, and from which its test items were developed. Previous studies have examined and described: (i) the development of reach and grasp skills of healthy, term-born infants (e.g.\(^ {30,34,40,96,157,179,180}\)); (ii) the early development of reaching in preterm infants (< 33 weeks gestational age; GA) compared to healthy, term-born infants\(^ {109,181}\); and (iii) the early development of UL behaviours in infants with neonatal stroke compared to healthy, term-born infants (< eight months C.A.\(^ {83,177}\)). Within this body of literature, three recent studies have informed the development of the GRAB. A randomised clinical trial investigated the impact of eight weeks of UL movement training on the emergence of reaching in preterm infants (n=26) and healthy, term-born infants (n=13) by determining the number and duration of unimanual hand-toy contacts.\(^ {109}\) The group that received UL movement training demonstrated: (i) increased frequency of hand-toy contacts; (ii) increased frequency in consistently reaching for toys; and (iii) increased percentage of time spent “interacting” with the toy.\(^ {109}\) A prospective study identified less bimanual midline toy manipulation in infants with stroke (n=8) compared to healthy, term-born (n=16 \(^ {177}\)). Another prospective study compared asymmetries of the orientation of hand and finger
movements in infants with stroke (n=13) and healthy, term-born infants (n=13) by evaluating hand orientation during GMs at fidgety age (12 weeks post-term). The degree of asymmetry identified in infants with stroke was highly predictive of later UCP. Based on the literature and supported by expert panel review, several unimanual and two bimanual UL behaviours were selected as criteria to measure early reach to grasp development on the GRAB at three assessment occasions: 14, 16 and 18 weeks C.A. These assessment occasions were selected based on literature reporting that healthy, term-born infants in Western cultures demonstrate pre-reaching movements (e.g. 24, 30) prior to reach onset from three to five months (e.g. 30, 32); and grasping as early as 4.5 months (e.g. 21, 35). The research team designed a structured play session to conduct at each assessment occasion, wherein infants would be seated in an infant chair and presented with three toys to elicit reaching and grasping. Behaviours were defined through discussion within the research team and with consultation with an expert panel, until 100% agreement was reached. The final GRAB criteria comprised the following reach and grasp behaviours: no unimanual activity, unimanual prehensile movements, unimanual transport phase, unimanual contribution to hands at midline, unimanual contact, unimanual grasp, other unimanual activity, bimanual midline grasp and bimanual midline behaviour. Behaviours were further categorised into ‘behavioural events’ (i.e. behaviour quantified by a discrete number of counts) or ‘behavioural duration’ (i.e. length of time in seconds that a behaviour was observed). The test items of time phase (TP) and toy colour phase (TCP) were then defined; whereby TP comprised six 30-second toy presentations, while TCP comprised three 30-second toy presentations, with each of the toys presented twice (see Table 4.1. for a graphical representation of TP and TCP items of the GRAB). The scoring method involved coding and recording each behaviour retrospectively from each video-recorded assessment occasion, using the free annotation software ELAN. Each behaviour was assigned a numerical code from zero to six; and each UL was scored separately using ELAN. The final scoring criteria (which includes definitions of each behaviour, as well as definitions for a ‘behavioural event’ and ‘behavioural duration’) of the GRAB are presented in Table 4.2.
Description of the structured play session

Infants were assessed at home, with a caregiver present, during the morning when they were in a calm and alert state. The structured play session involved a block design that comprised alternate 30-second periods of toy presentations and 30-second periods of no toy presentations by an occupational therapist. There were six periods of toy presentation (three minutes of toy presentation in total; and total session duration of 5.5 minutes). Infants were seated in a Baby Björn Babysitter Balance® infant chair and presented with three toys in a random order, (one toy per presentation). The toys were presented in the midline at shoulder height, approximately 75% of arm length, through an opening in the middle of a custom-built black cloth screen to minimise visual distractions. Each toy presentation provided an opportunity for the infant to unimanually and/or bimanually reach for, contact and/or grasp the toys within a 30-second period. The toys were briefly moved along a vertical or horizontal axis in the infant’s midline or visual field during a toy presentation to redirect their attention if they did not interact with the toy. The toys were similar in material, shape, size and appearance, differing only in colour combination. Colour combinations were coded based on the colour of the body and head of the toy (e.g. red/green, pink/orange and yellow/red; see Table 1 for pictures of the toys). The play session was filmed with one Sony Handycam DCR-SR68 video camera (approximately 1.2 metres above the infant) which captured a full view of infants, their ULs and the toys. A schematic drawing of the GRAB set-up is provided in the study protocol paper.58

Expert content review

An expert panel was consulted to review the test items (i.e. TP and TCP) of the GRAB. The panel comprised: (i) four senior occupational therapists, whose experience in paediatrics ranged from 15 to over 30 years; (ii) a senior physiotherapist with over 30 years’ experience in paediatrics; and (iii) a child neurologist with 13 years’ experience in paediatrics. Based on their clinical expertise, each member of the panel confirmed that the test items and structured play session of the GRAB should: (i) detect asymmetries in unimanual/bimanual reach and grasp behaviours between ULs in infants with asymBI; and (ii) detect differences in unimanual/bimanual reach and grasp behaviours between healthy, term-born infants and infants with asymBI.
Expert review of scoring criteria

The expert panel reviewed the scoring criteria of the GRAB. As a result of pilot scoring of 15 assessment occasions by the first author (M.P.; involving a combination of randomly selected healthy term-born infants and infants with asymBl at 14, 16 and 18 weeks C.A.), scoring difficulties were identified in interpreting whether a unimanual contact was ‘palmar’ or ‘dorsal’ based on hand orientation; and the scoring criteria were modified. The final scoring criteria included seven unimanual and two bimanual behaviours (Table 4.2.), which were further classified into nine unimanual and three bimanual behavioural events and behavioural duration (Tables 4.3., 4.4. and 4.5.) to quantify and evaluate early reach to grasp development.

Scoring of the video-recorded assessment occasion

The complete video-recorded assessment occasion (comprised of alternate 30-second periods of toy presentations and no toy presentations) was edited into six separate 30-second video clips for each toy presentation (one clip=700 frames) using QuickTime™ v.7.6.9 Pro. These video clips were then scored by one independent rater who was masked to developmental status.

Using the free annotation software ELAN, the following UL behavioural events and behavioural duration (in seconds) were recorded: (i) number and duration of unimanual contacts; (ii) number and duration of unimanual grasps; (iii) duration of no unimanual activity; (iv) duration of unimanual prehensile movements; (v) duration of unimanual transport phase; (vi) duration of unimanual contribution to hands at midline; (vii) duration of other unimanual activity; (viii) number and duration of bimanual midline grasps; and (ix) duration of bimanual midline behaviour. Proportion of time demonstrating UL behaviours was determined by calculating the duration of each behaviour (in seconds) as a percentage of total toy presentation time (180 seconds). The coded behaviours from each video clip, as well as proportion of total toy presentation time for each behaviour were then collated into a Microsoft Excel spreadsheet for each infant.

Duration of no activity indicated the period of time that an infant did not demonstrate upper limb activity in relation to the toy, whereas duration of unimanual activity indicated the period of time that an infant demonstrated upper limb activity with each upper limb in relation to the toy. If an infant demonstrated a short period of
no activity and a prolonged period of unimanual activity (or vice versa); a statistical
difference could be detected between these behaviours.

Unimanual behaviours were opposing variables within each limb (which may
overlap in time between limbs) and represented each upper limb demonstrating
behaviours, and could vary in frequency and duration. The nine unimanual
behaviours measured on the GRAB were: number of contacts, number of grasps,
duration of contacts, duration of grasps, duration of no activity, duration of prehensile
movements, duration of transport phase, duration of contribution to hands at midline,
and duration of other activity. Bimanual behaviours were overlapping variables and
represented both upper limbs demonstrating the same frequency and duration of
behaviours simultaneously. The three bimanual behaviours measured on the GRAB
were: number of grasps, duration of grasps, and duration of midline behaviour.

The total sum of the duration of each unimanual behaviour, for each UL,
reflected 100% of total toy presentation time. The total sum of the duration of
unimanual contribution to hands at midline (for each UL) was equivalent to the
duration of bimanual midline behaviour, and represented a proportion of total toy
presentation time.

An asymmetry index (AI) was calculated for number of unimanual contacts
and grasps, comparing ULs for each infant. The AI was calculated as the absolute
value of the difference in the number of unimanual contacts and grasps between
ULs, divided by the total number of contacts/grasps for both ULs. Based on cranial
ultrasound or neonatal MRI (confirmed by a neonatologist), ULs were classified as
potentially impaired or unimpaired in the asymBI group. For the asymBI group, $AI = \frac{|(I - U)|}{|(I + U)|}$; whereby $I$ refers to the impaired UL and $U$ refers to the unimpaired
limb. For the healthy group, $AI = \frac{|(L - R)|}{|(L + R)|}$; whereby $L$ refers to the left limb
and $R$ refers to the right UL. The range of AI was 0 to 1, with an AI of 0 indicating
complete symmetry between ULs and an AI of 1 indicating complete asymmetry
between ULs. The AI values for the number of unimanual contacts and grasps for
each group were then converted to a percentage (0-100%) to indicate the proportion
of total toy presentation time that unimanual contacts and grasps were asymmetric
between ULs.
Participants

Two groups of infants participated in this study. One group comprised 24 infants with asymBI and the other group comprised 20 healthy term-born infants. Both groups were studied at 14, 16 and 18 weeks C.A. to determine internal consistency of the GRAB. The final assessment occasion was chosen in this study to quantify reach and grasp behaviours within each group and to compare groups. The final assessment occasion was chosen for this study as it represents an age that maturing reach behaviours and emerging grasp behaviours have been reported in healthy, term-born infants (e.g. 24, 30, 32, 182, 183).

The asymBI group were recruited from four hospitals in south-east Queensland, Australia and from three sites in Pisa, Italy. Infants presented with clinical signs of a unilateral (one sided) or asymmetric (more involved on one side) brain lesion (e.g. arterial stroke, venous infarction, intraventricular haemorrhage or periventricular leukomalacia), which was confirmed from cranial ultrasound or neonatal MRI by a neonatologist. Infants were excluded if they had epileptic seizures and remained unstable on medication; and had co-morbidities such as visual and hearing impairments.58

The healthy, term-born group were recruited in south-east Queensland through convenience sampling. Infants with post-natal medical complications (e.g. jaundice) requiring extended hospital admission or medical treatments were excluded.58

Ethical approval was obtained from each hospital (HREC/09/QRCH/134, 1814MC, SSA/12/QGC/203); The University of Queensland (2009001870); and The University of Pisa (43/2011). Informed consent was obtained from the infants’ parents.58

Internal consistency of the GRAB

Internal consistency is the degree of interrelatedness among items in a measure.184 For this study, internal consistency refers to the consistency of UL behaviours within a single assessment occasion, which involved six 30-second toy presentations (i.e. consistency over time) and three toy colour presentations (i.e. consistency across toy colours). It was predicted that infants may have demonstrated a warm-up effect across the 30-second toy presentations (i.e. increasing behaviours over time) and may have preferred one toy colour combination
over another (i.e. more behaviours for one toy colour) within a single assessment occasion.

To determine internal consistency of the GRAB, 15 assessment occasions were randomly selected using a computer-generated random number sequence. The sample comprised a combination of assessment occasions at 14, 16 and 18 weeks C.A. (five from each assessment occasion) from 15 infants (six with asymBI and nine healthy, term-born). Internal consistency was determined by calculating Cronbach’s alpha coefficients, with each assessment occasion split into: (i) six time phases (TP), whereby one TP represented one 30-second trial of one toy presentation; and (ii) three toy colour phases (TCP), whereby one TCP represented two 30-second trials of the same toy colour presentation. All trials for each toy presentation for the 15 assessment occasions were scored by one independent rater.

Statistical analysis

Descriptive statistics are presented as mean (standard deviation) for continuous variables and as frequency (percentage) for categorical variables. Characteristics of infants with asymBI were compared with those of healthy infants using an independent samples t-test for continuous outcomes (i.e. gestational age) and a Fisher’s Exact Test for categorical outcomes (i.e. gender, side and type of brain lesion). The internal consistency for time phase and toy colour phase was determined by calculating Cronbach’s alpha coefficients. A Cronbach’s alpha coefficient value of 0.70 is considered acceptable, while values above 0.80 are preferable.

The association between UL (i.e. left and right for healthy group; potentially impaired and unimpaired for asymBI group) and number of unimanual contacts/grasps was investigated using mixed effects Poisson regression. Main effects included in the model were group (i.e. healthy/asymBI) and UL, and a group by UL interaction term was also included. Infant ID was included as a random effect to account for possible non-independence of outcomes within each infant. The association between group and number of bimanual midline grasps was investigated using Poisson regression. The healthy group was defined to be the reference group. Specifically, the potentially impaired UL from the asymBI group was compared to the left UL from the healthy group (as the latter was expected to be the non-dominant hand); and the potentially unimpaired UL from the asymBI group was compared to the right UL from the healthy group (as the latter was expected to be the dominant
hand). For within-group analyses, the right UL was used as the reference UL for the healthy group; and the unimpaired UL was used as the reference UL for the asymBI group. Where differences in duration of total toy presentations occurred (i.e. less than 180 seconds was captured), the logarithm of the actual duration of toy presentations was included as an offset in the Poisson model. Effect estimates calculated using Poisson models are reported as incidence rate ratios (IRR) with 95% confidence intervals (95% CIs).

Linear regression was used to investigate the association between group and AI for the number of unimanual contacts/grasps. The association between UL and the proportion of unimanual behaviours out of total toy presentation time (i.e. no activity, prehensile movements, transport phase, contribution to hands at midline, contacts, grasps and other activity) were investigated using a mixed effects linear regression. Association between group and the proportion of bimanual midline grasps/unimanual contribution to hands at midline out of total toy presentation time were investigated using a mixed effects linear regression, with infant ID included as a random effect. Effect estimates are reported as mean differences (MD). For all analyses a $p$-value < 0.05 was considered statistically significant. Analyses were conducted using Stata v.13.1.166

4.2.4. Results

Participants

Forty four infants participated in this study including 24 infants with asymBI (12 males, 50%) and 20 healthy, term-born infants (11 males, 55%). The asymBI group were born with a GA at birth between 27 and 41 weeks, while the healthy group were born with a GA at birth between 38 and 42 weeks. The GA of the asymBI group was significantly lower than for the healthy group (mean±SD=37±4.5 and 40±1.0 weeks respectively, $p$=0.006). Infants in the asymBI group predominantly had a unilateral left sided brain lesion (n=13), seven infants had bilateral asymmetric lesions, and four had a unilateral right sided brain lesion. The most common type of brain lesion was arterial stroke (14 infants, 58.3%); followed by intraventricular haemorrhage (IVH) and periventricular leukomalacia (PVL; 3 infants each, 12.5%); and one infant had a bilateral IVH with asymmetric PVL (4.2%).
Duration and scoring of video clips

There were incomplete video clips (video-recorded toy presentations) for six infants due to faulty video cameras or infants becoming irritable and/or fatigued during the assessment. For these infants, all available video clips were analysed. The median duration of video clips of all infants was 168 seconds, ranging from 29 to 175 seconds (out of a total possible 180 seconds of toy presentations).

The period of time required to score each participant’s video-recordings depended on the quantity and duration of their reach and grasp behaviours; ranging from 30 minutes to one hour.

Internal consistency of UL behaviours for time phase and toy colour phase

Internal consistency of each unimanual and bimanual UL behaviour for TP and TCP using Cronbach’s alpha coefficients are reported in Table 3. For TP, seven out of nine unimanual behavioural events/duration (i.e. number of contacts, number of grasps, duration of no activity, duration of prehensile movements, duration of transport phase, duration of grasps and duration of other activity); and two out of three bimanual behavioural events/duration (number of midline grasps and duration of midline behaviour) demonstrated good to very good internal consistency (alpha=0.72 to 0.89). Duration of no unimanual activity demonstrated the strongest internal consistency (alpha=0.89); whereas duration of unimanual contribution to hands at midline and duration of bimanual midline behaviour demonstrated the weakest internal consistency (alpha=0.50).

For TCP, six out of nine unimanual behavioural events/duration (i.e. number of contacts, number of grasps, duration of no activity, duration of prehensile movements, duration of transport phase and duration of contacts) demonstrated good internal consistency (alpha=0.73 to 0.82). Number of unimanual contacts and duration of unimanualprehensile movements demonstrated the strongest internal consistency (alpha=0.82). Similarly to the time phase, duration of unimanual contribution to hands at midline and duration of bimanual midline behaviour demonstrated the weakest internal consistency (alpha=0.46).

Unimanual contacts, grasps and bimanual grasps between and within groups

The association between group and number of unimanual contacts, grasps and bimanual grasps are reported in Table 4.4. and Figure 4.1. For the number of unimanual contacts, both groups were similar; and neither group demonstrated UL asymmetry. For the number of unimanual grasps, both groups were similar;
however, the asymBI group was less likely to use the impaired UL compared to the unimpaired UL (IRR=0.6, 95% CI 0.5 to 0.8, \( p < 0.001 \); Table 4.4. and Figure 4.1.). The healthy group were almost twice as likely to demonstrate bimanual midline grasps compared to the asymBI group (IRR=1.9, 95% CI 1.4 to 2.5, \( p < 0.001 \); Table 4.5., Figure 4.1.).

**Asymmetry Index for number of unimanual contacts and grasps between groups**

The associations between group and AI for the number of unimanual contacts and grasps are reported in Table 4.4., Appendix 4A.1. and 4A.2. For the number of unimanual contacts, the healthy group demonstrated asymmetry between ULs for 20% less of the time compared to the asymBI group (mean difference MD=-0.2, 95% CI -0.4 to 0.0, \( p=0.11 \)). For the number of unimanual grasps, both groups demonstrated asymmetry between ULs for 40% of the time (MD=0.0, 95% CI -0.2 to 0.3, \( p=0.93 \)).

**Proportion of time of unimanual reach and grasp behaviours between and within groups**

The association both between groups (healthy/asymBI) and within groups (potentially impaired vs unimpaired for asymBI; left vs right for healthy), with the proportion of time that unimanual reach and grasp behaviours were demonstrated are reported in Table 4.4. The asymBI group demonstrated a non-significantly smaller proportion of time for unimanual grasps (MD=9.8%, 95% CI -1.3 to 20.9, \( p=0.08 \)) compared to the healthy group. The asymBI group also demonstrated a smaller proportion of time for unimanual grasps using the impaired UL compared to the unimpaired UL (MD=-9.1%, 95% CI -16.6 to -1.7, \( p=0.02 \)).

**4.2.5. Discussion**

The GRAB demonstrated moderate to strong construct validity as it identified asymmetries between ULs for unimanual grasps and on the AI for unimanual contacts; and a paucity of bimanual grasps in infants with asymBI compared to healthy, term-born infants. There was no ‘warm-up effect’ identified on the GRAB, as the majority of reach and grasp behaviours were consistent across toy presentations and toy colours within an assessment occasion. The GRAB was able to detect and quantify the presence, absence and asymmetry of emerging unimanual and bimanual reach and grasp behaviours in infants with asymBI and healthy, term-born infants at 18 weeks C.A. A major finding of this study is that infants with asymBI
demonstrated a paucity of bimanual grasps when compared to healthy, term-born infants. Marked differences were detected for number of unimanual contacts on the AI and for bimanual midline grasps for infants with asymBI compared to healthy, term-born infants. Marked asymmetries between ULs were detected for unimanual grasping in infants with asymBI.

Previous studies have described reach to grasp development in healthy, term-born infants from three weeks up to one year (e.g.\textsuperscript{32,34,157}). Specifically, some studies have examined movement speed and movement quality during reaching using kinematic analysis\textsuperscript{32,157} and have measured the number of reaches towards a vertically moving toy (e.g.\textsuperscript{157}); or the number, duration and direction of reach towards a toy moving in a circular path (e.g.\textsuperscript{32}). Other studies have compared reach and grasp behaviours of preterm infants or infants with stroke to healthy, term-born infants as young as two to four months.\textsuperscript{109,181} Specifically, one study examined movement quality and anticipatory strategies during reaching towards a toy being moved in a semi-circular path across a magnetic surface\textsuperscript{181}; while another quantified the number and duration of toy contacts, number of reaches and examined hand orientation during toy contact towards a toy presented at the midline.\textsuperscript{109} In contrast, the present study examined only one time point for unimanual and bimanual reach and grasp behaviours (including the number of unimanual contacts, grasps and bimanual grasps) in infants with asymBI compared to healthy, term-born infants at 18 weeks C.A. This time point was chosen for this study as it represents an age that maturing reach behaviours and emerging grasp behaviours have been reported in healthy, term-born infants (e.g.\textsuperscript{24,30,32,182,183}). This work on the GRAB extends on previous work in early reaching\textsuperscript{178} by identifying asymmetries between the potentially impaired and unimpaired ULs in unimanual contacts and grasps; and a paucity of bimanual grasps in infants with asymBI compared to healthy, term-born infants.

In this study, the GRAB demonstrated strong internal consistency for several unimanual and bimanual reach and grasp behaviours for both TP and TCP test items within an assessment occasion. This finding confirms that both healthy, term-born infants and infants with asymBI did not demonstrate a warm-up effect over time, and did not demonstrate a preference for a particular coloured toy within an assessment occasion. In contrast, weak internal consistency was identified for: unimanual contribution to hands at midline, unimanual contacts, other unimanual activity, bimanual midline grasps and bimanual midline behaviour. Scoring of these
behaviours may have been impacted by reduced quality of video-recordings. For example, when both hands at the midline were occluded by the toy; unimanual behaviours may have been easier to identify compared to bimanual behaviours. In addition, the ability of the rater to identify when a unimanual or bimanual behaviour had commenced, ceased or changed may have been impacted by environmental factors within the home (e.g. lighting and space restrictions), which subsequently may have impacted on the set-up of equipment (e.g. camera angle and tripod height).

Previous research has reported that infants with perinatal or neonatal stroke, aged two to seven months C.A., demonstrate laterality of UL reaching to contact toys and less manipulation of toys in the midline compared to healthy, term-born infants. In the present study, the asymBI group demonstrated asymmetry between ULs for unimanual contacts for only 20% more of the time than the healthy group. The asymBI group also demonstrated a paucity of bimanual grasps compared to the healthy group at 18 weeks C.A. A possible explanation for this finding is that reach and grasp behaviours were only emerging in the asymBI group at 18 weeks C.A., which has been proposed in other studies (e.g. ). A paucity of UL behaviours in the asymBI group may also provide a possible explanation for the lack of asymmetries detected on the GRAB.

In the present study, the asymBI group demonstrated a similar frequency of unimanual contacts between the potentially impaired and unimpaired ULs, with few asymmetries detected on the GRAB. This finding lends support to previous research that reach and grasp behaviours are only emerging in infants with asymBI prior to six months C.A. (e.g. ). The asymBI group in this study, however, demonstrated marked asymmetries between the potentially impaired and unimpaired ULs for unimanual grasps. This finding may indicate an emerging hemiparesis, which needs to be confirmed with follow-up assessment at six and 12 months C.A.

Previous studies have reported that healthy, term-born infants do not yet demonstrate hand preference prior to six months of age (e.g. ). The present study confirmed this finding as the majority of healthy, term-born infants demonstrated a similar frequency of unimanual contacts and grasps between ULs.

The GRAB is quick to administer, requiring only three minutes of toy presentation within a total of 5.5 minutes of video time. In contrast, scoring of the GRAB requires at least 30 minutes depending on the quantity of an individual infant’s
reach and grasp behaviours, suggesting its utility is more likely within the research rather than clinical context. This study, identified weak internal consistency in some behaviours (e.g. other unimanual activity and bimanual midline behaviour), which may have been impacted by reduced quality of video-recordings due to environmental factors (e.g. lighting, space restrictions, camera angle and tripod height, as well as occlusion of hands at the midline by the toys). Future research is needed to: (i) evaluate intra- and inter-rater reliability and agreement of the GRAB; (ii) evaluate longitudinal development of behaviours across multiple assessment occasions rather than a single occasion; and (iii) investigate its association with other measures of UL reach and grasp behaviours.

Findings of this study suggest that the GRAB can be utilised as a quantitative measure of the presence or absence of: (i) unimanual reach and grasp behaviours of the potentially impaired and unimpaired ULs in infants with asymBI; and (ii) bimanual midline reach and grasp behaviours for both ULs together. A paucity rather than asymmetry of unimanual grasp may be indicative of an emerging hemiparesis. The GRAB provides an important contribution to the limited research in the area of very early detection of UCP by quantifying early reach to grasp development in infants.

Strengths of this study include evaluation at only one time point, based on the hypothesis that both healthy, term-born infants and infants with asymBI would demonstrate the most mature reach and emerging grasp at 18 weeks C.A.; and to reduce the potential confounding of age on developmental trajectories. Another strength of this study is that there was some heterogeneity of the asymBI sample (i.e. infants with unilateral and asymmetric bilateral brain lesions), which provides a more representative sample of this very young and at-risk population.

Potential limitations of this study were the relatively small sample size and scoring difficulties associated with the GRAB due to environmental factors (e.g. lighting, space restrictions, camera angle and tripod height, as well as occlusion of hands by toys), which resulted in reduced quality of video-recordings. These factors were addressed by standardising the equipment and set-up within each home between assessment occasions; conducting the assessment in a room or area of the home with minimal furniture; and monitoring of the video-recordings during each assessment by another therapist. Due to the relatively small sample size, it was not feasible to perform separate analyses of internal consistency for each group.
4.2.6. Conclusion

The GRAB demonstrated moderate to strong construct validity and strong internal consistency for both infants with asymBI and healthy, term-born infants. The GRAB is a consistent measure across toy presentations within an assessment occasion, as there was no toy preference or warm-up effect identified for either group. The GRAB can be utilised as a quantitative measure in a research setting for early detection of the presence or absence of unimanual and bimanual reach and grasp behaviours in infants who are at risk of UCP. In this study, the GRAB identified that infants with asymBI demonstrated a paucity of bimanual grasps compared to healthy, term-born infants; and that infants with asymBI demonstrate asymmetry between the potentially impaired and unimpaired ULs for unimanual grasps. Earlier detection of asymmetries between ULs in emerging reach and grasp behaviours in infants with asymBI will enable earlier referral to infant-friendly interventions. The next steps for the GRAB will be to: (i) measure and report its within-rater and between-rater reliability and agreement; (ii) evaluate longitudinal development of reach and grasp from 14 to 18 weeks C.A.; and (iii) determine if reach and grasp development can predict delayed fine motor development in infants with asymBI.
Table 4.1.
Toys used in the Grasp and Reach Assessment of Brisbane and a graphical representation of the time phase and toy colour phase test items.

<table>
<thead>
<tr>
<th>Play session</th>
<th>Description</th>
<th>Toys used in the play session</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>At each GRAB play session, three toys are presented through a screen. The toys are similar in shape, size and appearance, differing only in colour combination (e.g. red/green, pink/orange and yellow/red). The GRAB consists of two test items: TP and TCP. One GRAB assessment occasion comprises six TPs and three TCPs.</td>
<td><img src="image1" alt="red/green" /> <img src="image2" alt="pink/orange" /> <img src="image3" alt="yellow/red" /></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Test item</th>
<th>Description</th>
<th>Graphical representation</th>
</tr>
</thead>
<tbody>
<tr>
<td>TP</td>
<td>One 30-second trial consisting of a single toy presentation. <em>An example of a TP item: Presenting the pink/orange toy for 30 seconds (one trial).</em></td>
<td><img src="image4" alt="Example TP Toy" /></td>
</tr>
<tr>
<td>TCP</td>
<td>Two 30-second trials of the same toy presentation. <em>An example of a TCP item: Presenting the pink/orange toy for 60 seconds (two trials of 30 seconds).</em></td>
<td><img src="image5" alt="Example TCP Toys" /></td>
</tr>
</tbody>
</table>

Key. GRAB, Grasp and Reach Assessment of Brisbane; TP, Time Phase; TCP, Toy Colour Phase.
Table 4.2.  
Scoring criteria of the Grasp and Reach Assessment of Brisbane.

<table>
<thead>
<tr>
<th>Upper limb behaviour</th>
<th>Definition of upper limb behaviour</th>
<th>Scoring code*</th>
</tr>
</thead>
<tbody>
<tr>
<td>No unimanual activity</td>
<td>No anticipatory movements towards the toy (e.g. no excitable motoric actions) and no attempts to approach the toy (e.g. no prehensile hand or finger movements). Hand/arm may be static.</td>
<td>0</td>
</tr>
<tr>
<td>Unimanual prehensile movements</td>
<td>Anticipatory movements towards the toy (e.g. excitable motoric actions) and/or preparatory movements in an attempt to approach the toy (e.g. prehensile hand or finger movements).</td>
<td>1</td>
</tr>
<tr>
<td>Unimanual transport phase</td>
<td>Arm movements (e.g. swiping and reaching) towards the toy, in an attempt to contact the toy, without contacting the toy.</td>
<td>2</td>
</tr>
<tr>
<td>Unimanual contribution to hands at midline</td>
<td>Each hand is at the midline. Hands may be touching or clasped together, without contacting the toy.</td>
<td>3</td>
</tr>
<tr>
<td>Unimanual contact</td>
<td>Any contact initiated by the infant with any part of the toy (i.e. head, body, arms, hands, stick). If the assessor uses the toy to contact the infant’s hand or arm to capture attention, for instance, this is not considered a toy contact.</td>
<td>4</td>
</tr>
<tr>
<td><strong>Examples of toy contact:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infant’s hand is open, fingers are extended or flexed, and the surface of the hand makes contact with the toy;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infant’s hand is loosely closed with fingers flexed around the toy, and the surface of the hand makes contact with the toy;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infant’s hand is fist with fingers tightly flexed, and the surface of the hand makes contact with the toy.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unimanual grasp</td>
<td>Grasping the toy using all or most fingers with the palm, and closing around the toy. Grasping may be brief or the toy may be held for a prolonged period of time. The infant may also adjust his/her grasp around the toy; and/or manipulate the toy with finer movements around the toy’s head/arms/hands.</td>
<td>5</td>
</tr>
<tr>
<td>Other unimanual activity</td>
<td>An alternative arm/hand activity that is not directed towards the toy (e.g. hand out to side of torso, hand to mouth, contacting or grasping clothing).</td>
<td>6</td>
</tr>
<tr>
<td>Bimanual midline grasp</td>
<td>Grasping the toy with both hands simultaneously in the midline.</td>
<td>N/A</td>
</tr>
<tr>
<td>Bimanual midline behaviour</td>
<td>Both hands are at the midline. Hands may be touching or clasped together, without contacting the toy.</td>
<td>N/A</td>
</tr>
</tbody>
</table>
Table 4.2. (continued)

**Scoring criteria of the Grasp and Reach Assessment of Brisbane.**

<table>
<thead>
<tr>
<th>Further categorisation of upper limb behaviours</th>
<th>Definition of behaviour categories</th>
</tr>
</thead>
<tbody>
<tr>
<td>Behavioural event</td>
<td>A behaviour quantified by a discrete number of counts within an assessment occasion (total possible duration of 180 seconds (i.e. number of contacts and grasps)).</td>
</tr>
<tr>
<td>Behavioural duration</td>
<td>The duration in seconds that a behaviour was observed within an assessment occasion (total possible duration of 180 seconds; e.g. duration of contacts and grasps).</td>
</tr>
</tbody>
</table>

**Key.** GRAB, Grasp and Reach Assessment of Brisbane; N/A, not applicable. *The scoring code of 0-6 was used to retrospectively record each upper limb behaviour demonstrated by infants for each video-recorded toy presentation. For each assessment occasion, three toys were presented in a random order, with a total of six toy presentations. The total possible duration of toy presentation for each assessment occasion was three minutes out of a total video-recorded duration of 5.5 minutes.*
Table 4.3.  
Internal consistency of unimanual and bimanual behaviours during time phase and toy colour phase of the Grasp and Reach Assessment of Brisbane using Cronbach’s Alpha coefficients.

| Upper limb behaviour (n=15 assessment occasions/infants; 9 healthy, term-born and 6 with asymBI) | Cronbach’s Alpha | Cronbach’s Alpha |
| Unimanual behaviours | | |
| Number of contacts | 0.86 | 0.82 |
| Number of grasps | 0.77 | 0.73 |
| Duration of no activity | 0.89 | 0.80 |
| Duration of prehensile movements | 0.83 | 0.82 |
| Duration of transport phase | 0.85 | 0.79 |
| Duration of contribution to hands at midline | 0.50 | 0.46 |
| Duration of contacts | 0.62 | 0.63 |
| Duration of grasps | 0.86 | 0.76 |
| Duration of other activity | 0.72 | 0.51 |
| Bimanual behaviours | | |
| Number of midline grasps | 0.77 | 0.66 |
| Duration of midline grasps | 0.83 | 0.67 |
| Duration of midline behaviour | 0.50 | 0.46 |

Key. GRAB, Grasp and Reach Assessment of Brisbane; asymBI, asymmetric brain injury; TP, Time Phase test item; TCP, Toy Colour Phase test item.
Table 4.4.
Comparison of the Grasp and Reach Assessment of Brisbane mean scores between and within groups using incidence rate ratios or mean differences.

<table>
<thead>
<tr>
<th>Group</th>
<th>Limb</th>
<th>Unimpaired vs Impaired</th>
<th>Right vs Left</th>
<th>Unimpaired vs Right</th>
<th>Impaired vs Left</th>
</tr>
</thead>
<tbody>
<tr>
<td>asyMBI group</td>
<td>(n=24)</td>
<td>(n=20)</td>
<td>(n=24)</td>
<td>(n=44)</td>
<td></td>
</tr>
<tr>
<td>Number of contacts</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>IRR (95% CI)</td>
<td>p-value</td>
<td>IRR (95% CI)</td>
</tr>
<tr>
<td>Number of grasps</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>IRR (95% CI)</td>
<td>p-value</td>
<td>IRR (95% CI)</td>
</tr>
<tr>
<td>Number of activities</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>MD (95% CI)</td>
<td>p-value</td>
<td>MD (95% CI)</td>
</tr>
<tr>
<td>Duration of unimanual behaviour as a percentage of total toy presentation time</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>No activity</td>
<td>5.4 (11.6)</td>
<td>8.6 (16.5)</td>
<td>0.8 (3.4)</td>
<td>1.7 (6.5)</td>
<td>3.2 (-0.8,2.0)</td>
</tr>
<tr>
<td>Prehensile movements</td>
<td>0.7 (1.7)</td>
<td>1.6 (6.7)</td>
<td>1.7 (2.4)</td>
<td>3.7 (6.5)</td>
<td>0.9 (-1.9,3.7)</td>
</tr>
<tr>
<td>Transport phase</td>
<td>7.1 (5.6)</td>
<td>7.3 (6.6)</td>
<td>8.9 (4.3)</td>
<td>7.1 (4.6)</td>
<td>0.2 (-1.8,2.2)</td>
</tr>
<tr>
<td>Contribution to hands at midline</td>
<td>1.9 (3.2)</td>
<td>1.9 (3.2)</td>
<td>3.3 (5.9)</td>
<td>3.3 (5.9)</td>
<td>N/C</td>
</tr>
<tr>
<td>Contacts</td>
<td>10.6 (10.8)</td>
<td>11.9 (10.8)</td>
<td>11.3 (9.7)</td>
<td>11.1 (9.5)</td>
<td>1.3 (-1.8,4.3)</td>
</tr>
<tr>
<td>Grasps</td>
<td>23.3 (21.1)</td>
<td>14.2 (20.7)</td>
<td>23.5 (22.2)</td>
<td>24.2 (22.7)</td>
<td>-9.1 (-16.6, -1.7)</td>
</tr>
<tr>
<td>Other activity</td>
<td>51.0 (27.9)</td>
<td>54.5 (26.0)</td>
<td>50.7 (27.8)</td>
<td>49.1 (30.7)</td>
<td>3.5 (-5.0,11.9)</td>
</tr>
</tbody>
</table>

Key. GRAB, Grasp and Reach Assessment of Brisbane; asyMBI, asymmetric brain injury; IRR, incidence rate ratio; 95% CI, 95% confidence interval; SD, standard deviation; MD, mean difference; N/C, not calculated as contribution to hands at midline represents each upper limb demonstrating the same duration of midline behaviour; -,-, no values to report as the analysis only compared groups rather than limbs; * statistically significant result.
Table 4.5. *Comparison of the Grasp and Reach Assessment of Brisbane mean scores between groups using incidence rate ratios or mean differences.*

<table>
<thead>
<tr>
<th>Group</th>
<th>asymBI group (n=24)</th>
<th>Healthy group (n=20)</th>
<th>asymBI group vs Healthy group (n=44)</th>
<th>IRR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bimanual behaviour</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of midline grasps</td>
<td>4 (7)</td>
<td>7 (8)</td>
<td>1.9 (1.4, 2.5)</td>
<td>&lt;0.001*</td>
<td></td>
</tr>
<tr>
<td>Duration of bimanual behaviour</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>as a percentage of total toy</td>
<td>Midline grasps</td>
<td>7.2 (12.4)</td>
<td>11.9 (15.6)</td>
<td>0.27</td>
<td></td>
</tr>
<tr>
<td>presentation time</td>
<td>Midline behaviour</td>
<td>1.9 (3.2)</td>
<td>3.3 (5.9)</td>
<td>0.33</td>
<td></td>
</tr>
</tbody>
</table>

**Key.** GRAB, Grasp and Reach Assessment of Brisbane; asymBI, asymmetric brain injury; IRR, incidence rate ratio; 95% CI, 95% confidence interval; SD, standard deviation; MD, mean difference; * statistically significant result.
Figure 4.1. Scatter plots of number of unimanual contacts (with mean + SD) for each limb (A); and number of unimanual grasps (with mean + SD) for each limb with number of bimanual midline grasps (with mean + SD) for both limbs (B).

Key. asymBI (U), asymmetric brain injury group – unimpaired limb; asymBI (I), asymmetric brain injury group – impaired limb; asymBI (B), asymmetric brain injury group – bimanual midline grasps; healthy (R), healthy group – right limb; healthy (L), healthy group – left limb; healthy (B), healthy group – bimanual midline grasps.
Figure 4A.1. Scatter plot of the Asymmetry Index of total number of unimanual contacts (with mean + SD) between upper limbs for each group. Figure 4A.2. Scatter plot of the Asymmetry Index of total number of unimanual grasps (with mean + SD) between upper limbs for each group. Key. Healthy, healthy group – left vs right upper limbs; asymBI, asymmetric brain injury group – potentially impaired vs unimpaired upper limbs. Possible Asymmetry Index values ranged from 0 (symmetrical) to 1 (asymmetric), which were converted to a percentage (0-100%) to indicate proportion of total toy presentation time that unimanual behaviours were asymmetric between upper limbs (e.g. Asymmetry Index value of 0.5 for unimanual contacts in the asymBI group indicates asymmetry between the potentially impaired and unimpaired upper limbs for 50% of total toy presentation time).
4.3. Summary and conclusions

Key findings of this paper were:

- The GRAB demonstrated evidence of moderate to strong construct validity with existing literature as a quantitative measure of early reach and grasp behaviours in the absence of a published and validated measure of UL asymmetry in early reach and grasp behaviours in infants with asymBI who are younger than six months C.A.
- The GRAB demonstrated evidence of strong internal consistency as there was no warm-up effect identified across toy presentations within an assessment occasion in both infants with asymBI and healthy, term-born infants.
- Infants with asymBI and healthy, term-born infants both demonstrated emerging unimanual and bimanual reach and grasp behaviours at 18 weeks C.A.
- Infants with asymBI demonstrated a paucity rather than asymmetry of emerging unimanual and bimanual reach and grasp behaviours compared to healthy, term-born infants at 18 weeks C.A.
- The GRAB can quantify the presence or absence of early unimanual and bimanual reach to grasp development in infants with asymBI and healthy, term-born infants at 18 weeks C.A.

Chapter 4 addressed Aim 2 by presenting the first measurement paper on the GRAB, which reported its development, construct validity and internal consistency. As predicted in Hypothesis 2, the GRAB demonstrated evidence for moderate to strong construct validity and strong internal consistency for a majority of early reach and grasp behaviours. A major finding of this study was that infants with asymBI demonstrated less unimanual and bimanual reach and grasp behaviours compared to healthy, term-born infants. Furthermore, reach and grasp behaviours were only emerging in the participants of this study compared to previously published studies of infants at risk of UCP (i.e. preterm infants and/or infants with stroke compared to healthy, term-born infants).
The next step following validity testing of quantitative measures such as the GRAB is reproducibility testing. The next chapter addresses Aim 3 by presenting paper 4. This paper is the second measurement paper on the GRAB, which evaluates and reports its reproducibility (which involves intra- and inter-rater reliability and agreement).
Chapter 5: Reproducibility of the Grasp and Reach Assessment of Brisbane (GRAB)

5.1. Introduction to Chapter 5

This chapter addresses Aim 3 in the paper, ‘Intra-rater and inter-rater reliability of the Grasp and Reach Assessment of Brisbane (GRAB).’ This reproducibility study evaluates intra-rater and inter-rater reliability and agreement of the measurements on the GRAB. It was predicted that the GRAB would demonstrate evidence of strong intra- and inter-rater reliability and high percentage intra- and inter-rater agreement of measurements.

5.2. Paper 4: Intra-rater and inter-rater reliability of the Grasp and Reach Assessment of Brisbane (GRAB)

This paper was submitted to Research in Developmental Disabilities on 18\textsuperscript{th} February, 2015, and is currently under review.

Title

Intra- and inter-rater reproducibility of measurements on the Grasp and Reach Assessment of Brisbane (GRAB)

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Journal
Research in Developmental Disabilities

Key words
infant, upper extremity function, asymmetric brain injury, congenital hemiplegia, cerebral palsy, stroke, assessment, evaluative measure, rater agreement, reliability, reproducibility of measurements

Competing Interests
The authors declare they have no competing interests.
Authors’ Contributions
RNB is the Australian Research Council (ARC) chief investigator A and AG is the partner investigator on the study. RNB, AG and JZ were responsible for writing and obtaining the major study grant from the ARC. AG defined the original assessment protocol, and together with RNB, led the modification of the assessment protocol to the present design. RNB, AG, JZ and MP are responsible for all ethics applications and ethical reporting of the study outcomes. AG, VB, GT and MP led the modification of the assessment scoring protocol. MP and GS scored all assessment occasions for the reliability and agreement analyses. RSW provided guidance and assistance on statistical analysis. MP wrote the initial manuscript and all authors have read and approved the final manuscript.

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5.2.1. Abstract

The Grasp and Reach Assessment of Brisbane (GRAB) is a quantitative measure to detect asymmetries in reaching and grasping behaviours between upper limbs (UL) in infants with asymmetric brain injury (asymBI). This study reports the intra- and inter-rater reliability and agreement of measurements on the GRAB.

Unimanual and bimanual reaching and grasping behaviours were investigated in six infants with asymBI and seven healthy infants aged between 14 and 18 weeks C.A. in a structured play session. Behaviours including the number and duration of unimanual contacts, unimanual grasps, bimanual midline grasps; and duration of bimanual midline behaviour were measured. An occupational therapist and medical doctor were the independent raters. Intra-rater reliability and agreement were determined with one rater scoring 15 randomly selected video-recorded assessments on two occasions; and inter-rater reliability and agreement were determined with two raters scoring the same 15 video-recorded assessments on one occasion. Intra- and inter-rater reliability were determined by calculating intraclass correlation coefficients (ICC) for GRAB behaviour scores. Intra- and inter-rater agreement were determined by calculating the standard error of measurement (SEM) and smallest detectable difference (SDD); and presented using Bland-Altman plots.

The strongest intra-rater reliability for unimanual behaviours was for number of contacts, number and duration of grasps, and duration of contribution to hands at midline (i.e. each hand at the midline, without contacting the toy; ICC 0.91-0.99). The strongest inter-rater reliability for unimanual behaviours was for duration of grasps (ICC 0.94-0.97). Intra- and inter-rater reliability for bimanual behaviours were strong (0.78-0.98). Intra-rater agreement of 90% or higher was identified for number of: bimanual midline grasps (SEM 1.3, SDD 3.7); unimanual grasps (SEM 1.9, SDD 5.3); and unimanual contacts (SEM 2.8-3.0, SDD 7.6-8.3). Inter-rater agreement of 90% or higher was identified for number of: unimanual grasps (SEM 1.8-2.4, SDD 5.1-6.6); and bimanual midline grasps (SEM 2.0, SDD 5.6).

The GRAB demonstrated evidence for strong intra- and inter-rater reliability and agreement for quantifying emerging unimanual and bimanual reach and grasp behaviours in infants with asymBI, aged 14 to 18 weeks C.A.
5.2.2. Introduction

Reach to grasp development: early detection of asymmetries

Infants with asymmetric brain injury (asymBI), who are at high risk of hemiplegia, will have delayed development of bimanual coordination and an impaired ability to complete daily tasks.\textsuperscript{58} Detection of early asymmetries during upper limb (UL) motor development in infants with asymBI from two to seven months corrected age (C.A.) has been reported in a small number of studies.\textsuperscript{176-178,186,187} Other studies have compared reach to grasp development of preterm infants or infants with stroke to healthy, term-born infants aged two to seven months.\textsuperscript{109,177,181} Movement quality and anticipatory strategies during reaching for moving toys using kinematic analysis has been reported previously.\textsuperscript{181} Behavioural coding from video-recorded assessments to measure reaching to contact toys in the midline,\textsuperscript{109,178} or bimanual manipulation of toys in the midline\textsuperscript{177} has also been reported.

The laterality of ULs in reaching trajectories of infants with perinatal stroke and healthy infants aged between two and seven months C.A. was evaluated over a period of six months.\textsuperscript{178} Infants with perinatal stroke consistently demonstrated fewer reaches, of shorter duration, to contact toys in the midline, using the impaired UL compared to the unimpaired UL over time; and the reaching trajectory between ULs in infants with perinatal stroke was asymmetrical (n=6), in contrast to healthy infants, whose reaching trajectory between ULs was symmetrical (n=16). Longitudinal assessment of reaching trajectories in infants with perinatal stroke was recommended as an effective method of evaluating UL motor development in at-risk infants.\textsuperscript{178} There are, however, other UL behaviours that should also be considered for a more detailed evaluation of early UL motor development in infants at risk of hemiplegia, compared to healthy infants, such as unimanual prehensile movements and unimanual and bimanual grasping.\textsuperscript{21,30,46}

Measurement of early detection in at-risk infants

There is limited use of valid and reliable UL measures in current literature to detect hemiplegia in infants with asymBI, younger than 12 months C.A. The mini-Assisting Hand Assessment (mini-AHA) is currently the only valid measure reported for infants confirmed with congenital hemiplegia, aged eight to 18 months, to examine the use of their impaired UL during bimanual tasks. The mini-AHA is based on the Assisting Hand Assessment (AHA; for children with uCP and obstetric brachial plexus palsy, aged 18 months to 12 years), and involves a video-recorded,
semi-structured play session whereby toys (designed to elicit bimanual UL use)\textsuperscript{11,12} are provided to infants.\textsuperscript{12} The mini-AHA comprises 20 test items which are scored on a four-point rating scale, and from which raw scores are converted into logit scores (ranging from 0 to 100).\textsuperscript{12} Intra- and inter-rater reproducibility of the mini-AHA, however, are yet to be established.\textsuperscript{12} Earlier detection of asymmetries in emerging UL motor behaviours in infants with asymBI would enable timely referral to interventions.\textsuperscript{188} The Hand Assessment for Infants (HAI) is currently being developed for infants with asymBI, aged three to 12 months, to: (i) examine the quality of goal-directed unimanual and bimanual actions during play; and (ii) detect asymmetries between ULs.\textsuperscript{9,10} The HAI involves a video-recorded, semi-structured play session whereby toys (designed to elicit goal-directed unimanual and bimanual UL use) are provided to infants.\textsuperscript{9,10} The preliminary scale of the HAI comprises 18 items which are scored on a three-point rating scale.\textsuperscript{9} Each UL is scored separately on the HAI to reflect potential asymmetries between ULs, and both ULs are scored together to reflect bimanual UL use based on criterion and norm-reference scales.\textsuperscript{10} A preliminary Rasch analysis suggests promising results for validity of the HAI; however, intra-, inter-rater and test-retest reproducibility of the HAI are yet to be established.\textsuperscript{9}

An earlier study\textsuperscript{178} reported good inter-rater reliability (n=2 raters on one occasion) based on percentage agreement > 90% in 20% of all trials, based on behavioural coding from video-recorded assessments of number of reaches to toy contact and duration of hand-toy contacts. The reproducibility and clinical utility of behavioural coding to evaluate asymmetries between ULs during reaching in infants with perinatal stroke aged two to seven months remain unclear.\textsuperscript{178}

In the absence of a valid and reliable measure to detect asymmetries between ULs in emerging unimanual and bimanual reach and grasp behaviours in infants at risk of hemiplegia, younger than six months C.A., the Grasp and Reach Assessment of Brisbane (GRAB) was developed. The GRAB has demonstrated evidence for moderate to strong construct validity and strong internal consistency to quantify early detection of unimanual and bimanual reaching and grasping behaviours in infants with asymBI aged 18 weeks C.A.; and identified a paucity of emerging unimanual and bimanual reaching and grasping in infants with asymBI compared to healthy infants, at 18 weeks C.A.\textsuperscript{188} Intra- and inter-rater reproducibility of measurements on the GRAB, however, is unknown.
Reproducibility comprises both: (i) reliability, which involves the consistency of measurements, despite measurement error\textsuperscript{189}; and (ii) agreement, which measures the degree of similarity between repeated measurements, based on measurement error.\textsuperscript{190-192} The intraclass correlation coefficient (ICC) is commonly used as a measure of reliability and consists of a ratio of the variance as a result of between-participant variability (true score variance) and variance in measurements (true score variance and measurement error).\textsuperscript{193} The ICC is reported on a dimensionless scale, ranging from 0 to 1. The ICC is, however, heavily influenced by the heterogeneity of the sample population and should not be used on its own to represent the precision of scores between repeated measurements.\textsuperscript{190,191} In contrast, agreement is not influenced by the heterogeneity of a sample and estimates the measurement error.\textsuperscript{190-192} The standard error of measurement (SEM) is a useful parameter of agreement, and is reported in the unit of interest.\textsuperscript{190,191} This study reports and evaluates the intra-rater (n=1 rater on two occasions) and inter-rater (n=2 raters on one occasion) reliability and agreement of measurements on the GRAB.

5.2.3. Method
Participants

The sample population of this study consisted of six infants with asymBI and seven healthy, term-born infants, studied at 14, 16 and/or 18 weeks C.A. The gestational age (GA) of infants ranged from 27 to 42 weeks. The study sample was therefore heterogeneous. Ethical approval was obtained from four hospitals in south-east Queensland, Australia (HREC/09/QRCH/134, 1814MC, SSA/12/QGC/203); The University of Queensland (2009001870); and three sites in Pisa, Italy (43/2011). Informed consent was obtained from infants’ parents. Full methodology is provided in the study protocol paper.\textsuperscript{58}

Task description

The task description and equipment set-up of the GRAB have been described in greater detail elsewhere.\textsuperscript{188} Briefly, infants were assessed at home and seated in a Baby Björn Babysitter Balance® infant chair. They were presented with three toys in the midline, in a random order, for six 30-second trials (total time of one assessment=180 seconds). The task was filmed with a video camera (approximately 1.2 metres above the infant) which captured a full view of infants, their ULs and the toys.
Scoring of video-recorded assessments

Video-recorded assessments were edited into six video-clips for each toy presentation using QuickTime Pro™ v.7.6.9. The following outcomes were assessed independently by two raters who were masked to developmental history: (i) number and duration of unimanual contacts; (ii) number and duration of unimanual grasps; (iii) duration of no unimanual activity; (iv) duration of unimanual prehensile movements; (v) duration of unimanual transport phase; (vi) duration of unimanual contribution to hands at midline (i.e. each hand at the midline, without contacting the toy); (vii) duration of other unimanual activity (i.e. an alternative UL activity that was not directed towards the toy); (viii) number and duration of bimanual midline grasps; and (ix) duration of bimanual midline behaviour. Outcomes were recorded using the free annotation software ELAN. Scores from each video-clip were then collated into a Microsoft Excel spreadsheet.

Behaviours were then categorised into a ‘behavioural event’ or ‘behavioural duration’. A behavioural event was defined as “a behaviour quantified by a discrete number of counts within a 180-second assessment” (i.e. number of contacts and grasps), and a behavioural duration was defined as “the length of time in seconds that a behaviour was observed out of a total possible assessment time of 180 seconds”.

Procedure for reproducibility of video-recorded assessments

Fifteen video-recorded assessments (5 at 14 weeks, 5 at 16 weeks and 5 at 18 weeks) were randomly selected from both groups (six infants with asymBI and seven healthy, term-born infants) using a computer-generated randomisation sequence. Given that infants had three video-recorded assessments each (one for each time point); it was possible that some infants may have had more than one video-recorded assessment included within this random sample.

Intra-rater reproducibility was performed by one rater (occupational therapist) who was masked to developmental history, by scoring each of the 15 video-recorded assessments on two occasions, within a time interval of two to four weeks. Inter-rater reproducibility was performed by two raters (occupational therapist and medical doctor) who were masked to developmental history, by independently scoring each of the 15 video-recorded assessments on one occasion.
Data analysis

Descriptive statistics are presented as mean (standard deviation; SD) for continuous variables and as frequency (percentage) for categorical variables. Intra-rater and inter-rater reliability were determined using ICCs, derived from a mixed regression model.\textsuperscript{167,168} The ICC(3,1) model was selected as raters were not sampled.\textsuperscript{167,168} Reliability was evaluated using the following criteria: ICC > 0.90, very strong reliability; ICC 0.75-0.90, strong reliability; and ICC < 0.75, weak to moderate reliability.\textsuperscript{167,169}

Agreement was determined by: (i) calculating the mean difference (MD) between ratings, SD of the differences, and the 95% limits of agreement (LoA); (ii) calculating the standard error of measurement (SEM); and comparing the SEM to the smallest detectable difference (SDD). The 95% LoA was calculated to assess the degree of difference in GRAB scores between ratings and was estimated as the mean score±1.96*standard deviation of the mean score.\textsuperscript{170,171} The SEM was calculated to determine precision of GRAB scores\textsuperscript{190,191} between ratings and was estimated as the square root of the mean square error of the residuals.\textsuperscript{191} The SDD was calculated to ascertain the smallest difference in GRAB scores that would be considered significant, based on the formula 1.96*√2*SEM.\textsuperscript{191} Level of agreement was classified according to a priori criteria: ≥ 90%, high agreement; < 90%, low to moderate agreement; and an SDD of 10% based on the mean score of rating 1 for each UL behaviour demonstrated by the right UL. Three graphical representations are included as examples of intra-rater and inter-rater agreement using Bland-Altman plots. Analyses were performed using Stata v.13.\textsuperscript{166} Graphpad Prism™ was used to produce Bland-Altman plots.

5.2.4. Results

Participants

Thirteen infants participated in this reproducibility study and were assessed at 14, 16 and/or 18 weeks C.A. Six infants had an asymBI and seven were healthy, term-born infants (9 males, 69%). Infants with an asymBI predominantly had a unilateral left stroke (n=3); followed by a unilateral right stroke (n=1), a bilateral asymmetric stroke (n=1), and the remaining infant had a bilateral intraventricular haemorrhage and an asymmetric periventricular leukomalacia (n=1). The mean±SD GA of infants was 38±4 weeks.
Reproducibility of video-recorded assessments

Fifteen randomly selected video-recorded assessments were analysed for intra-rater and inter-rater reproducibility. Intra-rater reliability was strongest for behavioural duration (out of a total possible assessment duration of 180 seconds), specifically for duration of unimanual grasps and duration of unimanual contribution to hands at midline (ICC 0.95-0.99); followed by duration of bimanual midline grasps and duration of bimanual midline behaviour (ICC 0.95-0.98). Intra-rater reliability was also very strong for the following behavioural events: number of unimanual contacts, number of unimanual grasps, and number of bimanual midline grasps (ICC 0.91-0.97). Inter-rater reliability was strongest for behavioural duration only, specifically for duration of unimanual grasps (ICC 0.94-0.97); followed by duration of unimanual contribution to hands at midline, bimanual midline grasps and bimanual midline behaviour (ICC 0.90). Intraclass coefficients are reported in Table 5.1. for intra-rater reliability and in Table 5.2. for inter-rater reliability.

Intra-rater agreement was highest for behavioural events only, specifically for number of unimanual grasps and number of bimanual midline grasps (SEM ranging from one to two grasps, and SDD ranging from six to eight grasps); followed by number of unimanual contacts (SEM ranging from two to three contacts, and SDD ranging from seven to nine contacts). Inter-rater agreement was also highest for behavioural events only, specifically for number of unimanual and bimanual midline grasps (SEM ranging from one to three grasps, and SDD ranging from five to seven grasps). The parameters for determining agreement (MD between ratings, 95% LoA, SEM and SDD) are reported in Table 5.1. for intra-rater agreement and in Table 5.2. for inter-rater agreement. Three examples of agreement are presented as Bland-Altman plots in Figure 5.1. (i.e. intra-rater agreement for unimanual contacts and grasps using the right UL and bimanual midline grasps using both ULs) and Figure 5.2. (i.e. inter-rater agreement for unimanual contacts and grasps using the right UL and bimanual midline grasps using both ULs). Agreement for duration of each UL behaviour are presented as Bland-Altman plots in Appendix 5.1. (intra-rater agreement) and Appendix 5.2. (inter-rater agreement).
5.2.5. Discussion

The GRAB demonstrated evidence of strong intra- and inter-rater reliability and high intra- and inter-rater agreement to quantify emerging unimanual and bimanual reaching and grasping of toys in infants with asymBI and healthy, term-born infants.

Findings of the present study suggest that: (i) the measurement of behavioural events such as the number of unimanual and bimanual midline grasps, followed by the number of unimanual contacts; and (ii) the measurement of behavioural duration for unimanual grasping, unimanual contribution to hands at the midline, bimanual midline grasping and bimanual midline behaviour, are the most consistently measured UL behaviours for infants with asymBI and healthy, term-born infants within a 180-second video-recorded assessment on the GRAB. Secondly, findings suggest that the number of unimanual and bimanual midline grasps (behavioural events) are the most accurately observed UL behaviours for detecting asymmetries between ULs demonstrated by infants within a 180-second video-recorded assessment on the GRAB, and scored by one rater across two occasions, as well as two raters on a single occasion. Thirdly, findings suggest that emerging bimanual UL behaviours (i.e. number and duration of bimanual grasps and duration of bimanual midline behaviour), as well as emerging unimanual UL behaviours (i.e. number and duration of unimanual grasps, number of unimanual contacts and duration of unimanual contribution to hands at the midline) are more consistently measured and/or accurately observed in infants compared to other emerging unimanual UL behaviours that were also measured on the GRAB (i.e. prehensile movements, the transport phase, no activity and other activity).

No unimanual activity and other unimanual activity demonstrated the weakest intra- and inter-rater reliability and the lowest intra-rater and inter-rater agreement; and may have been more subject to interpretation by individual raters, depending on their clinical expertise. Unimanual prehensile movements and the transport phase may have also been more subject to interpretation by individual raters; or may have been more difficult to observe from the video-recordings and analyse using the ELAN software compared to bimanual behaviours. In addition, these unimanual UL behaviours may have been more sensitive to scoring difficulties related to reduced quality of video-recordings, due to environmental factors within the home (e.g. lighting, space restrictions), and/or set-up of equipment (e.g. camera angle and
tripod height). If the video-recordings were compromised by the environment or set-up of equipment during the assessment, the ability of the raters to identify and record when such behaviours had commenced, ceased or changed may have been impacted.

Previous studies have compared reach to grasp development of preterm infants or infants with stroke to healthy, term-born infants aged two to four months\textsuperscript{109,181}, using kinematic analysis\textsuperscript{181} or behavioural coding from video-recorded assessments.\textsuperscript{109,177,178} Although these studies quantified reach and grasp behaviours, they did not determine validity or reproducibility of the tools as outcome measures. The most recent of these studies\textsuperscript{178} reported good inter-rater reliability (n=2 raters on a single occasion) based on percentage agreement > 90% in 20% of all trials, whereby number of reaches to toy contact and duration of hand-toy contacts were measured. The reproducibility of behavioural coding\textsuperscript{178} is unclear, however, as no further information regarding the procedure and statistical analysis of determining reliability was provided. To date, the mini-Assisting Hand Assessment (mini-AHA) is the only valid measure to examine the use of the impaired UL during bimanual tasks in infants with a confirmed diagnosis of UCP younger than two years C.A.\textsuperscript{11,12} Intra- and inter-rater reproducibility of the mini-AHA, however, are yet to be established.\textsuperscript{12} The Hand Assessment for Infants (HAI) is currently being developed and validated for infants with asymBI, younger than 12 months C.A., to examine the quality of goal-directed unimanual and bimanual actions during play; and detect asymmetries between ULs.\textsuperscript{151} In contrast to previous studies, the present study is the first to investigate intra-rater and inter-rater reproducibility of the GRAB, which has previously demonstrated evidence for moderate to strong construct validity and strong internal consistency to detect emerging unimanual and bimanual reach and grasp behaviours in infants with asymBI compared to healthy, term-born infants, younger than six months C.A.\textsuperscript{188}

It was necessary in the present study to investigate agreement as well as reliability of measurements on the GRAB, for the following reasons: (i) the SEM is suitable for determining precision of scores between repeated measurements for an evaluative measure, such as the GRAB\textsuperscript{191}; (ii) the SDD indicates that differences between scores lower than the SDD for each UL behaviour are not discernible from measurement error; and (iii) Bland-Altman plots present a graphical format of the degree of similarity in scores between ratings, the presence of bias and outliers, and
the presence of a relationship between the variance in mean scores that is easy to interpret.\textsuperscript{171}

In the present study, for unimanual behaviours, the largest SEM and the smallest ICC were identified for duration of other unimanual activity demonstrated by the left UL; and the second largest SEM was identified for duration of other unimanual activity demonstrated by the right UL. This behaviour is potentially the most subjective and least accurately observed UL behaviour to measure on the GRAB; and may be influenced by the level of the rater’s clinical expertise.

The GRAB has demonstrated evidence of strong reliability and high agreement for the measurement of unimanual and bimanual midline grasping (both as behavioural events and behavioural duration); and strong reliability for the measurement of the number of unimanual contacts and duration of unimanual contribution to hands at the midline in infants with asymBI and healthy, term-born infants.

Potential limitations of this study include the small and heterogeneous sample size; and some scoring difficulties on the GRAB due in part by reduced quality of video-recordings, which may have been impacted by environmental factors within the home and/or set-up of equipment. This was addressed by standardising the equipment and set-up within each home between assessment occasions and monitoring of the video-recordings during each assessment by another therapist. Other scoring difficulties identified on the GRAB, irrespective of standardising the equipment and set-up within the home, were related to specific unimanual UL behaviours that were measured on the GRAB. Such behaviours included no unimanual activity, other activity, prehensile movements and the transport phase; which may have been more difficult to interpret or classify from video-recordings and code using the ELAN software compared to bimanual behaviours. Although the sample was adequate for an initial reproducibility analysis on the GRAB and provided evidence of strong reliability and high agreement for unimanual and bimanual grasping and midline behaviour; further work with a larger sample, comparing reproducibility of measurements on the GRAB between infants with asymBI and healthy infants, is required.
5.2.6. Conclusion

The GRAB demonstrated evidence for strong intra- and inter-rater reliability and high intra- and inter-rater agreement for detecting emerging unimanual and bimanual reaching to grasp toys in infants with asymBI and healthy, term-born infants. The use of valid and reliable measures to detect and evaluate asymmetries in emerging UL motor behaviours is needed for infants who are at risk of UCP, to enable earlier referral to interventions and to determine efficacy of interventions. The next step for the GRAB will be to examine and describe the longitudinal UL motor development (including development of reach to grasp behaviours) of infants with asymBI compared to healthy, term-born infants.
<table>
<thead>
<tr>
<th>GRAB behaviour</th>
<th>Unimanual behaviours (number)</th>
<th>Unimanual behaviours (duration in seconds)</th>
<th>Bimanual behaviours (number)</th>
<th>Bimanual behaviours (duration in seconds)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rating One:</td>
<td>Rating Two:</td>
<td>Between ratings: Right UL</td>
<td>Rating One:</td>
</tr>
<tr>
<td></td>
<td>Right UL Mean (SD)</td>
<td>Right UL Mean (SD)</td>
<td>ICC (95% CI)</td>
<td>MD (95% LoA)</td>
</tr>
<tr>
<td>Intra-rater reliability and agreement (n=1 rater on 2 occasions) of the Grasp and Reach Assessment of Brisbane for unimanual and bimanual reach to grasp behaviours.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**GRAB behaviour**

**Unimanual behaviours (number)**

- Contacts
  - Rating One: 22 (18)
  - Rating Two: 17 (15)
  - Between ratings: Right UL
  - Mean (SD) 14.2 (-28.0, 56.4)
  - ICC (95% CI) 0.55 (0.30, 0.81)
- Grasps
  - Rating One: 7 (6)
  - Rating Two: 6 (6)
  - Between ratings: Right UL
  - Mean (SD) 7.8 (12.8)
  - ICC (95% CI) 0.97 (0.94, 0.99)

**Unimanual behaviours (duration in seconds)**

- No activity
  - Rating One: 21.9 (26.3)
  - Rating Two: 7.7 (18.7)
  - Between ratings: Right UL
  - Mean (SD) 14.7
  - ICC (95% CI) 0.55 (0.30, 0.81)
- Prehensile movements
  - Rating One: 6.2 (8.2)
  - Rating Two: 4.1 (8.6)
  - Between ratings: Right UL
  - Mean (SD) 2.4
  - ICC (95% CI) 0.91 (0.85, 0.97)
- Transport phase
  - Rating One: 17.1 (10.2)
  - Rating Two: 13.8 (11.1)
  - Between ratings: Right UL
  - Mean (SD) 13.4 (10.0)
  - ICC (95% CI) 0.95 (0.91, 0.98)
- Contribution to hands at the midline
  - Rating One: 8.1 (12.1)
  - Rating Two: 7.4 (12.2)
  - Between ratings: Right UL
  - Mean (SD) 7.6
  - ICC (95% CI) 0.97 (0.94, 0.99)

**Key.** GRAB, Grasp and Reach Assessment of Brisbane; UL, upper limb; ICC, intraclass coefficient; 95% CI, ninety five percent confidence interval; MD, mean difference; 95% LoA, ninety five percent limits of agreement; SEM, standard error of measurement; SDD, smallest detectable difference; SD, standard deviation; -, no values to report as this analysis compared bimanual behaviour (both limbs together) between ratings rather than unimanual behaviour (each limb separately).
## Table 5.2.
**Inter-rater reliability and agreement (n=2 raters on 1 occasion) of the Grasp and Reach Assessment of Brisbane for unimanual and bimanual reach to grasp behaviours.**

<table>
<thead>
<tr>
<th>GRAB behaviour</th>
<th>Right UL</th>
<th>Right UL</th>
<th>Between raters: Right UL</th>
<th>Left UL</th>
<th>Left UL</th>
<th>Between raters: Left UL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>ICC (95% CI)</td>
<td>MD (95% LoA)</td>
<td>SEM</td>
<td>SDD</td>
<td>ICC (95% CI)</td>
</tr>
<tr>
<td><strong>Unimanual behaviours (number)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contacts</td>
<td>22 (18)</td>
<td>10 (10)</td>
<td>0.78 (0.64, 0.92)</td>
<td>12 (-6, 30)</td>
<td>6.4</td>
<td>17.7</td>
</tr>
<tr>
<td>Grasps</td>
<td>7 (7)</td>
<td>5 (6)</td>
<td>0.86 (0.78, 0.95)</td>
<td>2 (-5, 9)</td>
<td>2.4</td>
<td>6.6</td>
</tr>
<tr>
<td><strong>Unimanual behaviours (duration in seconds)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No activity</td>
<td>21.9 (26.3)</td>
<td>18.8 (20.3)</td>
<td>0.81 (0.68, 0.93)</td>
<td>3.4 (-24.9, 32.3)</td>
<td>10.0</td>
<td>27.6</td>
</tr>
<tr>
<td>Prehensile movements</td>
<td>6.2 (8.2)</td>
<td>13.3 (11.0)</td>
<td>0.81 (0.68, 0.93)</td>
<td>-7.1 (-19.0, 4.7)</td>
<td>4.1</td>
<td>11.4</td>
</tr>
<tr>
<td>Transport phase</td>
<td>17.1 (10.2)</td>
<td>13.7 (7.0)</td>
<td>0.51 (0.23, 0.77)</td>
<td>3.4 (-13.7, 20.4)</td>
<td>6.0</td>
<td>16.5</td>
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<tr>
<td>Contribution to hands at the midline</td>
<td>8.1 (12.1)</td>
<td>10.2 (15.4)</td>
<td>0.90 (0.84, 0.97)</td>
<td>-2.0 (-13.9, 9.8)</td>
<td>4.1</td>
<td>11.5</td>
</tr>
<tr>
<td>Contacts</td>
<td>21.6 (15.8)</td>
<td>11.7 (10.5)</td>
<td>0.80 (0.67, 0.93)</td>
<td>9.9 (-6.8, 26.6)</td>
<td>5.8</td>
<td>16.1</td>
</tr>
<tr>
<td>Grasps</td>
<td>22.2 (24.5)</td>
<td>25.8 (29.3)</td>
<td>0.94 (0.90, 0.98)</td>
<td>-3.6 (-22.0, 14.7)</td>
<td>6.4</td>
<td>17.7</td>
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<tr>
<td>Other activity</td>
<td>71.5 (34.0)</td>
<td>77.4 (25.0)</td>
<td>0.81 (0.69, 0.93)</td>
<td>-5.9 (-42.0, 30.1)</td>
<td>12.6</td>
<td>34.8</td>
</tr>
<tr>
<td><strong>Bimanual behaviours (number)</strong></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Midline grasps</td>
<td>4 (5)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>3 (4)</td>
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<td><strong>Bimanual behaviours (duration in seconds)</strong></td>
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<td></td>
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<tr>
<td>Midline grasps</td>
<td>10.4 (20.3)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>9.2 (15.8)</td>
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<tr>
<td>Midline</td>
<td>8.1 (12.1)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>10.2 (15.4)</td>
<td>0.90 (0.84, 0.97)</td>
</tr>
</tbody>
</table>

**Key:** GRAB, Grasp and Reach Assessment of Brisbane; UL, upper limb; ICC, intraclass coefficient; 95% CI, ninety five percent confidence interval; MD, mean difference; 95% LoA, ninety five percent limits of agreement; SEM, standard error of measurement; SDD, smallest detectable difference; SD, standard deviation; -, no values to report as this analysis compared bimanual behaviour (both limbs together) between ratings rather than unimanual behaviour (each limb separately).
Figure 5.1. Intra-rater agreement of the range of differences between ratings against range of mean scores of ratings (n=1 rater on 2 occasions) for number of unimanual right upper limb contacts (A); number of unimanual right upper limb grasps (B); and number of bimanual midline grasps (C) presented as Bland-Altman plots with 95% limits of agreement.
Figure 5.2. Inter-rater agreement of the range of differences between raters against range of mean scores of raters (n=2 raters on 1 occasion) for number of unimanual right upper limb contacts (A); number of unimanual right upper limb grasps (B); and number of bimanual midline grasps (C) presented as Bland-Altman plots with 95% limits of agreement.
Appendix 5.1. Intra-rater agreement of the range of differences between ratings against range of mean scores of ratings (n=1 rater on 2 occasions) for duration of no unimanual activity for the right upper limb (A.1); no unimanual activity for the left upper limb (A.2); duration of unimanual prehensile movements for the right upper limb (A.3); duration of unimanual prehensile movements for the left upper limb (A.4); duration of unimanual transport phase for the right upper limb (A.5); duration of unimanual transport phase for the left upper limb (A.6); unimanual contribution to hands at midline for the right upper limb (A.7); and unimanual contribution to hands at the midline for the left upper limb (A.8) presented as Bland-Altman plots with 95% limits of agreement.
Appendix 5.1. (continued). Intra-rater agreement of the range of differences between ratings against range of mean scores of ratings (n=1 rater on 2 occasions) for duration of unimanual contacts for the right upper limb (A.9); duration of unimanual contacts for the left upper limb (A.10); duration of unimanual grasps for the right upper limb (A.11); duration of unimanual grasps for the left upper limb (A.12); duration of other unimanual activity for the right upper limb (A.13); duration of other unimanual activity for the left upper limb (A.14); duration of bimanual grasps (A.15); and duration of midline behaviour (A.16) presented as Bland-Altman plots with 95% limits of agreement.
Appendix 5.2. Inter-rater agreement of the range of differences between raters against range of mean scores of raters (n=2 raters on 1 occasion) for duration of no unimanual activity for the right upper limb (B.1); no unimanual activity for the left upper limb (B.2); duration of unimanual prehensile movements for the right upper limb (B.3); duration of unimanual prehensile movements for the left upper limb (B.4); duration of unimanual transport phase for the right upper limb (B.5); duration of unimanual transport phase for the left upper limb (B.6); unimanual contribution to hands at midline for the right upper limb (B.7); and unimanual contribution to hands at the midline for the left upper limb (B.8) presented as Bland-Altman plots with 95% limits of agreement.
Appendix 5.2. (continued). Inter-rater agreement of the range of differences between raters against range of mean scores of raters (n=2 raters on 1 occasion) for duration of unimanual contacts for the right upper limb (B.9); duration of unimanual contacts for the left upper limb (B.10); duration of unimanual grasps for the right upper limb (B.11); duration of unimanual grasps for the left upper limb (B.12); duration of unimanual grasps for the right upper limb (B.11); and duration of unimanual grasps for the left upper limb (B.12); duration of other unimanual activity for the right upper limb (B.13); duration of other unimanual activity for the left upper limb (B.14); duration of bimanual grasps (B.15); and duration of midline behaviour (B.16) presented as Bland-Altman plots with 95% limits of agreement.
5.3. Summary and conclusions

Key findings of this paper were:

- The GRAB demonstrated evidence of strong intra- and inter-rater reliability and high intra- and inter-rater agreement to quantify three emerging reach and grasp behaviours: (i) unimanual grasping; (ii) bimanual grasping; and (iii) midline behaviour in both infants with asymBI and healthy, term-born infants at 14, 16 and 18 weeks C.A.

- The number of unimanual grasps, bimanual midline grasps and duration of bimanual midline behaviour were the most consistently measured indicators to quantify emerging reach and grasp behaviours in infants with asymBI and healthy, term-born infants at 14, 16 and 18 weeks C.A. on the GRAB.

- Behavioural events (i.e. behaviours quantified by a discrete number of counts) such as the number of unimanual grasps and bimanual midline grasps were the most accurately observed UL behaviours for detecting asymmetries between ULs in both infants with asymBI and healthy, term-born infants (scored by one rater across two occasions, as well as two raters on a single occasion) at 14, 16 and 18 weeks C.A. on the GRAB.

Chapter 5 addressed Aim 3 by presenting paper 4, the second measurement paper of the GRAB, which evaluated and reported its intra- and inter-rater reliability and agreement. It was predicted that the GRAB would demonstrated evidence of strong reliability and high percentage agreement for the measurement of early unimanual and bimanual reach and grasp behaviours. In this study, however, the GRAB only demonstrated evidence of strong reliability and high percentage agreement for grasping and midline behaviours. A major finding of this study was that the measurement of behavioural events such as unimanual and bimanual grasping were the most consistently measured UL behaviours on the GRAB.

The next chapter addresses Aim 4 by presenting paper 5, which is the third measurement paper of the GRAB. This paper examines the longitudinal development of reach to grasp in infants with asymBI compared to healthy infants, in relation to prediction of motor development at six and 12 months C.A. on the BSID III.
Chapter 6: Evaluation of longitudinal reach to grasp development on the Grasp and Reach Assessment of Brisbane as a method to predict delayed motor development

6.1. Introduction

This chapter addresses Aim 4 in the first draft of the final measurement paper of the GRAB; ‘Longitudinal development of reach to grasp and prediction of delayed motor development in infants with asymmetric brain injury’. This study examines the longitudinal development of reach and grasp behaviours at 14, 16 and 18 weeks C.A. on the GRAB, in relation to prediction of delayed motor development at six and 12 months C.A. on the BSID III in infants with asymBI compared to healthy infants. It was predicted that there would be differences in reach and grasp behaviours between infants with asymBI and healthy infants, as well as asymmetries between ULs in infants with asymBI at 14, 16 and 18 weeks C.A. These differences on the GRAB were anticipated to predict delayed motor development in infants with asymBI compared to healthy infants at six and 12 months C.A. on the BSID III.

6.2. Paper 5: Longitudinal development of reach to grasp and prediction of delayed motor development in infants with asymmetric brain injury

This paper will be submitted to Early Human Development in July 2016, once data analysis has been completed. For the first draft of the paper, the entire sample is included for GRAB data at 14, 16 and 18 weeks C.A., and for BSID III FM and GM data at six months C.A. The sample is incomplete for BSID III FM and GM data at 12 months C.A., with all available data included at the time of thesis submission.

Title
Assessment of reach to grasp to determine delayed motor development in infants with asymmetric brain injury

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Competing Interests
The authors declare they have no competing interests.

Authors’ Contributions
RNB is the Australian Research Council (ARC) chief investigator A and AG is the partner investigator on the study. RNB, AG and JZ were responsible for writing and obtaining the major study grant from the ARC. AG defined the original assessment protocol, and together with RNB, led the modification of the assessment protocol to the present design. RNB, AG, JZ and MP are responsible for all ethics applications and ethical reporting of the study outcomes. AG, VB, GT and MP led the modification of the assessment scoring protocol. MP, GT and VB collected the data. MP scored all assessment occasions for the analyses. RSW provided guidance and assistance on statistical analysis. MP wrote the initial manuscript and all authors have read and approved the final manuscript.

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6.2.1. Abstract

Background: Infants with asymmetric brain injury (asymBI) are at risk for Unilateral Cerebral Palsy (UCP), which involves delayed upper limb (UL) motor development. Longitudinal assessment of UL motor behaviours in combination with a standardised motor scale may be a useful method for predicting delayed motor development in at-risk infants.

Aims: To determine if emerging reach to grasp behaviours from 14 to 18 weeks corrected age (C.A.) can predict delayed FM and GM development at six and 12 months C.A. in infants with asymBI compared to healthy, term-born infants.

Study design: Prospective longitudinal study.

Subjects: 32 infants with asymBI and 20 healthy, term-born infants.

Outcome measures: The Grasp and Reach Assessment of Brisbane (GRAB) at 14, 16 and 18 weeks C.A. and the Bayley Scales of Infant and Toddler Development (BSID III) Motor Scale at six and 12 months C.A.

Results: Infants with asymBI demonstrated asymmetric unimanual contacts and grasps from 14 to 18 weeks C.A., and a paucity of bimanual grasps at 18 weeks C.A. (IRR=1.3, 95%CI 1.0-1.6, \( p=0.04 \)) compared to healthy infants on the GRAB. Infants with asymBI scored significantly lower on the BSID III Motor Scale at six and 12 months C.A. (e.g. at 12 months; FM raw scores, mean difference MD=8.1, 95%CI 6.3-9.8, \( p<0.0001 \)) compared to healthy infants. The number of unimanual contacts, grasps and bimanual grasps at 18 weeks C.A. on the GRAB were strong predictors of FM development on the BSID III for infants with asymBI at six months C.A. and not at 12 months C.A. (e.g. bimanual grasps as a predictor of FM scores \( r=0.3, 95\%CI 0.1-0.4, p=0.001 \)). The BSID III underestimated FM and GM impairment as only three infants (12%) with clinical signs of UCP were identified with FM and GM delay at six months C.A.; and only one infant was identified at 12 months C.A. The GRAB detected asymmetries in unimanual contacts and grasps from 14 to 18 weeks C.A. and a paucity of unimanual grasps at 14 weeks C.A. (IRR=0.3, 95%CI 0.12-0.93, \( p=0.04 \)) in infants with clinical signs of UCP compared to those without at six months C.A.

Conclusions: The GRAB can detect asymmetries in UL reach to grasp behaviours from 14 to 18 weeks C.A. and has potential to predict delayed motor development at six months C.A. in infants who are at risk of UCP.
6.2.2. Introduction

Infants at risk of unilateral cerebral palsy

One to two of every 1000 infants have an asymmetric brain injury (asymBI\textsuperscript{4}; e.g. intraventricular haemorrhages, periventricular leukomalacia, arterial strokes and venous infarctions) at birth.\textsuperscript{59} Although these infants are likely to develop Unilateral Cerebral Palsy (UCP) by 12 months of age\textsuperscript{58}, a definitive diagnosis may not be given until two or three years of age.\textsuperscript{177} Earlier detection of emerging asymmetries during upper limb (UL) motor development in infants at risk of UCP would enable earlier diagnosis and timely referral to early intervention.\textsuperscript{58,187}

Measurement of reach and grasp behaviours

A new measure, the Grasp and Reach Assessment of Brisbane (GRAB), has demonstrated evidence of construct validity and intra- and inter-rater reproducibility to quantify early reach to grasp development.\textsuperscript{188,194} When assessed on the GRAB, infants with asymBI demonstrated a paucity of reaching and grasping behaviours compared to healthy, term-born infants at 18 weeks corrected age.\textsuperscript{188} The measurement of behavioural events (behaviours quantified by a discrete number of counts, such as reaching to contact or grasp toys) demonstrated stronger reliability compared to the measurement of behavioural duration (length of time in seconds that behaviours were observed) on the GRAB.\textsuperscript{194} The number of contacts or grasps may be more representative of early reaching and grasping of toys rather than the length of time that a toy is touched or grasped.

Early longitudinal upper limb development and detection of delayed fine motor development

There is a body of literature that has examined the early development of reaching in preterm infants (< 33 weeks gestational age; GA) compared to healthy, term-born infants. Findings indicate that preterm infants have: (i) less organised UL movements and laterality of ULs in reaching\textsuperscript{195}; (ii) less effective reaching strategies\textsuperscript{181,196}; (iii) slower UL movements and increased adjustments during reaching\textsuperscript{197}; (iv) impaired motor planning\textsuperscript{198}; (v) impaired motor control\textsuperscript{199}; and (vi) increased risk of motor coordination delays and impaired manual dexterity.\textsuperscript{200}

\textsuperscript{4} Abbreviations: asymBI, asymmetric brain injury; BSID III, Bayley Scales of Infant and Toddler development; C.A., corrected age; CI, confidence interval; CP, cerebral palsy; FM, fine motor; GA, gestational age; GM, gross motor; GRAB, Grasp and Reach Assessment of Brisbane; HAI, Hand Assessment of Infants; IRR, incidence rate ratio; L, left upper limb; MD, mean difference; r, regression coefficient; R, right upper limb; SD, standard deviation; UL, upper limb.
There remains, however, a paucity of literature examining the early development of reaching in infants with early brain injury. Compared to healthy, term-born infants, infants with stroke aged two to seven months demonstrate: (i) asymmetric reaching between the unimpaired and impaired ULs; less bimanual midline manipulation; and (iii) achieve significantly lower fine motor (FM), gross motor (GM) and motor composite scores on the Bayley Scales of Infant and Toddler Development, version three (BSID III). A combination of a standardised assessment such as the BSID III and a simple video assessment of bimanual midline behaviour can be used to detect motor impairment in infants at risk of CP prior to 12 months of age. Although asymmetries between ULs in infants with stroke may be inconsistent in early infancy; consistent asymmetries can be detected by monitoring reaching trajectories from two to seven months of age. At present there are only two assessments (both under development) that have the potential to quantify asymmetries between ULs or examine the quality of bimanual performance in infants prior to 12 months C.A. at risk of UCP – the GRAB (from 3.5 to 4.5 months C.A.) and the Hand Assessment of Infants (HAI; from three to 12 months C.A.).

The present study extends our previous work utilizing the measurement of behavioural events to evaluate and quantify emerging reach to grasp development; and aims to compare the longitudinal development of infants with asymBI to healthy, term-born infants. The frequency and amount of change of unimanual and bimanual reach to grasp at 14, 16 and 18 weeks C.A. on the GRAB are compared to FM, GM and overall motor development at six and 12 months C.A. on the Bayley Scales of Infant and Toddler Development, version three (BSID III). This study also aims to determine if the number of unimanual contacts and grasps at 18 weeks C.A. on the GRAB can predict FM development at six and 12 months C.A. on the BSID III. It was hypothesised that infants with asymBI, compared to healthy, term-born infants, would demonstrate fewer unimanual contacts and grasps at 18 weeks C.A. on the GRAB; and would have suspected delays in motor development at six and 12 months C.A. on the BSID III.

6.2.3. Method

Participants

Infants were recruited from November 2010 until December 2014. The sample population comprised: (i) infants with asymBI receiving treatment and recruited from four major hospitals in south-east Queensland, Australia and from two major
hospitals and a tertiary institute in Italy; and (ii) healthy, term-born infants recruited through convenience sampling. Inclusion criteria for the asymBI group were: (i) clinical signs of a unilateral or asymmetric brain lesion (including arterial stroke, grade III or IV intraventricular haemorrhage and/or periventricular leukomalacia), confirmed from cranial ultrasound and/or neonatal MRI by a neonatologist; and (ii) living within a 200-kilometre radius of the Royal Brisbane and Women’s Hospital, Brisbane, Australia. Exclusion criteria for the asymBI group were: (i) epileptic seizures that were unresponsive to treatment; (ii) hydrocephalus requiring a shunt; and (iii) retinopathy of prematurity ≥ grade III. Inclusion criteria for the healthy, term-born group were: (i) Between 38 and 42 weeks GA; (ii) an uncomplicated delivery; and (iii) living within a 50-kilometre radius of the Royal Brisbane and Women’s Hospital, Brisbane, Australia. Exclusion for the healthy, term-born group involved the presence of post-natal complications requiring extended hospital admission and/or medical treatment. Ethical approval was obtained from the four hospitals in south-east Queensland, Australia (HREC/09/QRCH/134, 1814MC, SSA/12/QGC/203); The University of Queensland (2009001870); and the three sites in Italy (43/2011). Informed consent was obtained from infants’ parents prior to data collection.58

**The Grasp and Reach Assessment of Brisbane (GRAB)**

The task description and equipment set-up of the GRAB have been described in detail elsewhere.58 Briefly, infants were assessed at home while seated in a Baby Björn Babysitter Balance® infant chair by an occupational therapist. They were presented with three toys in the midline, in a block design consisting of six 30-second trials of toy presentation, separated by five 30-second trials of no toy presentation (total toy presentation time of three minutes within 5.5 minutes of video time). Video-recorded assessments were edited into six separate video-clips for each 30-second toy presentation using QuickTime™ Pro v.7.6.9.159 The following UL behavioural events were recorded by one rater who was masked to developmental history: (i) number of unimanual contacts; (ii) number of unimanual grasps; and (iii) number of bimanual grasps, using the free annotation software ELAN.160,161 Asymmetry was based on the side of the brain lesion (e.g. left brain lesion corresponded to a potentially impaired right UL), and also represented the lack of symmetry between ULs during unimanual UL behaviours.
The Bayley Scales of Infant and Toddler Development (BSID III)

The BSID III is a norm-referenced, standardized developmental assessment\(^{48,49}\) used to detect developmental delay in infants and young children from one to 42 months of age.\(^{162}\) In this study, fine motor (FM), gross motor (GM) and overall motor development of each infant were assessed by an occupational therapist using the Motor Scale.\(^{49}\) Differences in FM and GM development between groups over time were determined by calculating scaled scores for the FM and GM subtests (ranging from one to 19, with mean±standard deviation [SD] of 10±3). Overall motor development for each infant was determined by calculating motor composite scores (ranging from 40 to 160, with mean±SD of 100±15). Infants in this study who achieved less than seven FM or GM scaled scores and/or less than 85 motor composite scores (i.e. at least one SD below the mean), in comparison to normative data were considered to have suspected delays in FM, GM and/or overall motor development.\(^{48,49}\)

Statistical analysis

Descriptive statistics are presented as mean±SD for continuous variables and as frequency (percentage) for categorical variables. Characteristics of infants with asymBI were compared with those of healthy infants using an independent samples t-test for continuous outcomes (e.g. gestational age and actual age at assessment) and a Fisher's Exact Test for categorical outcomes (e.g. gender, side and type of brain lesion, and parental cultural background). The frequency of unimanual and bimanual reach to grasp on the GRAB was determined by calculating the mean number of unimanual contacts/grasps and bimanual grasps at each assessment occasion (14, 16 and 18 weeks), in each group.

The association between UL (i.e. left and right for the healthy group; potentially impaired and unimpaired for the asymBI group) and number of unimanual contacts/grasps/bimanual grasps over time was investigated using mixed effects Poisson regression. Main effects included in the model were group (i.e. healthy/asymBI) and UL, and a group by UL interaction term was also included. Infant ID was included as a random effect to account for possible non-independence of outcomes within each infant. The association between group and number of unimanual contacts/grasps/bimanual grasps over time was investigated using Poisson regression. For between-group analyses, the asymBI group was defined to be the reference group. For within-group analyses, the potentially unimpaired UL
was compared to the potentially impaired UL in the asymBI group; and the right UL was compared to the left UL in the healthy group. Effect estimates calculated using Poisson models are reported as incident rate ratios (IRR) with 95% confidence intervals (95% CIs).

The associations between group (i.e. healthy/asymBI) and FM and GM raw/scaled/motor composite scores at and between six and 12 months C.A. on the BSID III Motor Scale were investigated using linear regression. The association between number of unimanual contacts/grasps/bimanual grasps at 18 weeks C.A., and all Motor Scale scores at six and 12 months C.A. for each group were investigated using linear regression. Effect estimates are reported as mean differences (MDs) or regression coefficients ($r$) with 95% CIs. For all analyses, a $p$-value < 0.05 was considered statistically significant. Analyses were performed using Stata v.13.1.166

6.2.4. Results

The sample population comprised 32 infants with asymBI and 20 healthy, term-born infants assessed at 14, 16 and 18 weeks C.A. on the GRAB and at six and 12 months C.A. on the BSID III. Healthy, term-born infants and infants with asymBI were similar in gender and ethnicity (Table 6.1.). The asymBI group had a younger GA at birth compared to the healthy group ($p$=0.001); and four infants with asymBI were born very preterm (< 30 weeks GA). Based on cranial ultrasound or neonatal MRI, infants in the asymBI group predominantly had unilateral left sided brain lesions (16 participants, 50%), six infants had unilateral right sided brain lesions (19%), and the remaining ten infants had bilateral asymmetric lesions (31%). Parents of the healthy, term-born infants completed a much higher level of education compared to the parents of infants with asymBI ($p$ < 0.001).

Unimanual contacts, grasps and bimanual grasps between and within groups over three time points on the GRAB

The frequency of unimanual contacts, grasps and bimanual grasps were compared between groups (healthy versus asymBI) and/or within groups (right UL vs left UL for healthy; potentially unimpaired UL vs potentially impaired UL for asymBI); at each assessment occasion (14, 16 and 18 weeks C.A.) and between assessment occasions. There was some missing data due to missed appointments and/or study drop outs: three participants at 14 weeks C.A. (two healthy infants and one infant with asymBI); six at 16 weeks C.A. (one healthy infant and five infants with asymBI);
and one infant with asymBI at 18 weeks C.A. Data are presented in Table 6.2., Figure 6.1. and Figure 6.2.

Both groups demonstrated a similar frequency of unimanual contacts at 14, 16 and 18 weeks C.A. (Table 6.2. and Figure 6.1.). The healthy group was initially more likely to use the right UL compared to the left UL (at 14 weeks C.A.; IRR=1.4, 95% CI 1.1 to 1.7, \( p=0.001 \)). The asymBI group was initially more likely to use the unimpaired UL compared to the impaired UL (e.g. at 14 weeks C.A.; IRR=1.3, 95% CI 1.1 to 1.5, \( p < 0.001 \)).

The healthy group demonstrated a greater increase in frequency of unimanual contacts from 16 to 18 weeks C.A. (IRR=1.5, 95% CI 1.3 to 1.7, \( p < 0.001 \)), compared to the asymBI group. Neither group demonstrated differences between ULs in the frequency of unimanual contacts from 14 to 16 weeks C.A. and from 14 to 18 weeks C.A. (Table 6.2. and Figure 6.1.).

Both groups demonstrated a similar frequency of unimanual grasps at 14, 16 and 18 weeks C.A. (Table 6.2. and Figure 6.1.). The healthy group was initially more likely to use the right UL compared to the left UL (at 14 weeks C.A.; IRR=1.4, 95% CI 1.1 to 2.0, \( p=0.02 \)). Conversely, the asymBI group was more likely to use the unimpaired UL compared to the impaired UL later (at 18 weeks C.A.; IRR=1.2, 95% CI 1.1 to 1.5, \( p=0.03 \)).

The healthy group demonstrated a greater increase in frequency of unimanual grasps from 16 to 18 weeks C.A. (IRR=1.4, 95% CI 1.1 to 1.7, \( p=0.01 \)), compared to the asymBI group. Only the healthy group demonstrated a difference between ULs (i.e. the right UL grasped the toy less than the left UL from 14 to 16 weeks C.A. and more than the left UL from 16 to 18 weeks C.A.; Table 6.2. and Figure 6.1.)

The healthy group demonstrated more bimanual grasps compared to the asymBI group at 18 weeks C.A. (IRR=1.3, 95% CI 1.0 to 1.6, \( p=0.04 \)). Neither group demonstrated differences in the frequency of bimanual grasps between assessment occasions (Table 6.2. and Figure 6.2.).

Comparison of FM, GM subtest scores and motor composite scores between and within groups over time on the BSID III

Fine motor (FM) and gross motor (GM) subtest scores, as well as motor composite scores were compared between and within groups on the BSID III. There was some missing data due to study drop outs or due to participants who had only
been assessed on the BSID III at 6 months C.A. and were not yet 12 months C.A.: seven participants at 6 months C.A. (one healthy infant and six infants with asymBI); and 14 infants with asymBI at 12 months C.A. Data are presented in Table 6.3. and Figure 6.3.

The healthy group achieved significantly higher FM scores, GM scores and motor composite scores compared to the asymBI group at six and 12 months C.A. on the BSID III, except for FM raw scores at six months C.A. For example, the MD between groups was 2.9 FM scaled scores at 12 months C.A. (95% CI 1.3 to 4.4, \( p = 0.001 \)).

The healthy group demonstrated significant increases in FM and GM raw scores from six to 12 months C.A., for example, for FM raw scores (MD=8.9, 95% CI 7.5 to 10.3, \( p < 0.001 \)). The asymBI group also demonstrated significant increases in FM and GM raw scores from six to 12 months C.A., for example, for FM raw scores (MD=8.1, 95% CI 6.3 to 9.8, \( p < 0.001 \)).

**Comparison of Motor Scale scores for each group with the normative group of the BSID III**

The Motor Scale (i.e. FM, GM subtest and motor composite) scores for each healthy, term-born infant and infant with asymBI were compared to the BSID III normative mean scores from the United States at six and 12 months C.A.; and are presented in Figure 6.3.

For the FM subtest at six months C.A., all healthy, term-born infants and 14 infants with asymBI scored within the normative range (above seven scaled scores). At 12 months C.A., 18 healthy, term-born infants and eight infants with asymBI scored within the normative range. Based on the normative cut-off scores, only six infants with asymBI had suspected FM delay; five at six months C.A. and one at 12 months C.A.

For the GM subtest at six months C.A., all healthy, term-born infants and 14 infants with asymBI scored within the normative range (above seven scaled scores). At 12 months C.A., 18 healthy, term-born infants and eight infants with asymBI scored within the normative range. Based on the normative cut-off scores, only four infants had suspected GM delay; two with asymBI at six months C.A. and one from each group at 12 months C.A.

For the Motor Scale overall at six months C.A., all healthy, term-born infants and 14 infants with asymBI scored within the normative range (above 85 motor
composite scores). At 12 months C.A., 18 healthy, term-born infants and eight infants with asymBI scored within the normative range. Based on the normative cut-off scores, 16 infants had suspected overall motor delay: nine infants with asymBI at six months C.A.; six infants with asymBI and one healthy, term-born infant at 12 months C.A.

**Clinical outcomes of asymBI group on the BSID III and unimanual behaviour on the GRAB**

Clinical signs of UCP were identified by expert clinicians based on performance on the BSID III Motor Scale, during follow up assessments at six and 12 months C.A.

Of the 26 infants with asymBI who returned for follow-up assessment with the BSID III at six months C.A.; six (23%) demonstrated clinical signs of UCP. Of the remaining 20 infants with asymBI, one (4%) demonstrated clinical signs of spastic diplegia, one had a diagnosis of CP, and 18 (69%) did not demonstrate clinical signs of UCP at six months C.A. Only three infants (12%) with asymBI who demonstrated clinical signs of UCP had suspected FM delay at six months C.A. based on the BSID III.

Of the 18 infants with asymBI who returned and were due for follow-up assessment with the BSID III at 12 months C.A.; five (28%) demonstrated clinical signs of UCP, one (6%) with clinical signs of spastic diplegia, and another (6%) with a diagnosis of CP. The remaining 11 infants (60%) did not have a diagnosis of CP and/or did not demonstrate clinical signs of UCP at 12 months C.A. Only the infant who demonstrated clinical signs of spastic diplegia had suspected FM delay at 12 months C.A. based on the BSID III.

A post-hoc analysis (Poisson regression) was undertaken to compare unimanual behaviours between and within subgroups in the asymBI group from 14 to 18 weeks C.A. on the GRAB (i.e. infants with clinical signs of UCP and those without; Appendix 6A. and 6B.). Infants with UCP were less likely to demonstrate unimanual grasps compared to those without UCP at 14 weeks C.A. (IRR=0.3, 95% CI 0.12 to 0.93, p=0.04). In addition, infants with UCP demonstrated a marked asymmetry between ULs, using the impaired UL less than the unimpaired UL for both unimanual contacts and grasps (e.g. unimanual grasps at 16 wks C.A.; IRR=0.03, 95% CI 0.003 to 0.2, p < 0.001). Data are presented in Appendix 6A. and 6B.
Prediction of motor development on the BSID III

The relationship between the number of unimanual contacts, grasps and bimanual grasps on the GRAB with FM and GM subtest scores on the BSID III was examined; and is presented in Table 6.4.

In the healthy group, the number of unimanual contacts and grasps were not strong predictors of FM scores on the BSID III. The number of unimanual contacts was, however, a strong predictor of: (i) GM raw and scaled scores for both ULs at 6 months C.A. (e.g. for the right UL \( r=0.1, 95\% \text{ CI } 0.02 \text{ to } 0.2, p=0.02 \)); and (ii) GM raw scores for the left UL at 12 months C.A. (\( r=0.14, 95\% \text{ CI } 0.02 \text{ to } 0.3, p=0.03 \)).

The number of unimanual grasps was a strong predictor of GM raw scores for both ULs only at 12 months C.A. (e.g. for the left UL \( r=0.2, 95\% \text{ CI } 0.1 \text{ to } 0.3, p=0.01 \)). In contrast, the number of unimanual contacts was a strong predictor in the asymBI group of: (i) FM raw scores for the potentially impaired UL (\( r=0.1, 95\% \text{ CI } 0.02 \text{ to } 0.2, p=0.03 \)); (ii) FM scaled scores for both ULs (e.g. for the left UL \( r=0.2, 95\% \text{ CI } 0.1 \text{ to } 0.3, p=0.004 \)); and (iii) motor composite scores for both ULs only at 6 months C.A. (e.g. for the left UL \( r=0.6, 95\% \text{ CI } 0.1 \text{ to } 1.1, p=0.02 \)). The number of unimanual grasps was also a strong predictor of: (i) FM raw and scaled scores for both ULs (e.g. for the left UL \( r=0.2, 95\% \text{ CI } 0.1 \text{ to } 0.4, p=0.01 \)); and (ii) motor composite scores for both ULs only at 6 months C.A. (e.g. for the left UL \( r=1.2, 95\% \text{ CI } 0.5 \text{ to } 1.9, p=0.002 \)).

In the healthy group, the number of bimanual grasps was not a strong predictor of FM scores at six or 12 months C.A. on the BSID III; however, it was a strong predictor of GM raw scores only at 12 months C.A. (\( r=0.3, 95\% \text{ CI } 0.2 \text{ to } 0.5, p < 0.001 \)). In contrast, the number of bimanual grasps was a strong predictor in the asymBI group of: (i) FM raw scores (\( r=0.2, 95\% \text{ CI } 0.1 \text{ to } 0.4, p=0.01 \)); (ii) FM scaled scores (\( r=0.3, 95\% \text{ CI } 0.1 \text{ to } 0.4, p=0.001 \)); (ii) GM scaled scores (\( r=0.2, 95\% \text{ CI } 0.03 \text{ to } 0.3, p=0.02 \)); and (iii) motor composite scores (\( r=1.3, 95\% \text{ CI } 0.6 \text{ to } 2.0, p=0.001 \)) only at 6 months C.A.

6.2.5. Discussion

The findings of the present longitudinal study suggest that infants with asymBI demonstrated asymmetric unimanual reach to grasp development from 14 to 18 weeks C.A. on the GRAB. Compared to healthy infants, however, infants with asymBI demonstrated a paucity rather than asymmetry of unimanual grasping; and a paucity of bimanual grasping at 18 weeks C.A. on the GRAB. Secondly, findings
suggest that, although infants with asymBI scored significantly lower on the BSID III Motor Scale compared to healthy, term-born infants; the BSID III underestimates FM impairment in infants with clinical signs of UCP at 12 months C.A. Thirdly, our findings suggest that the number of unimanual contacts, grasps and bimanual grasps at 18 weeks C.A. on the GRAB are strong predictors of FM, GM and overall motor performance at 6 months C.A. on the BSID III for infants with asymBI.

Previous research has identified that: (i) infants aged two to seven months C.A. with stroke demonstrate laterality of ULs in reaching to contact toys and less frequent manipulation of toys in the midline compared to healthy, term-born infants; and (ii) children aged four to eight years who were born preterm (<33 weeks GA) demonstrate laterality of ULs during reaching compared to healthy children born at term. Findings of this study lend support to and extend on this earlier work by identifying asymmetries between ULs in unimanual contacts as early as 14 weeks C.A. and unimanual grasps at 18 weeks C.A. in infants with asymBI; and detecting a paucity of bimanual grasps in infants with asymBI at 18 weeks C.A. compared to healthy, term-born infants on the GRAB.

A previous study has reported that asymmetries in wrist movements at fidgety age on the GMs can indicate an emerging hemiparesis in infants with neonatal stroke younger than six months C.A. Findings of this study extend on this earlier work by identifying asymmetries in unimanual contacts and grasps at 14, 16 and 18 weeks C.A.; and a paucity of unimanual grasps at 14 weeks C.A. on the GRAB in infants with clinical signs of UCP at six months C.A.

An interesting finding was that healthy, term-born infants demonstrated less unimanual reaching and grasping at 16 weeks C.A.; and subsequently demonstrated more unimanual change from 14 to 18 weeks C.A. compared to infants with asymBI on the GRAB. Infants may have demonstrated other UL behaviours not associated with reach to grasp which were not identified on the GRAB, which may reflect a limitation of this measure.

Both healthy, term-born infants and infants with asymBI demonstrated sequential improvements on the BSID III for FM and GM subtests from six to 12 months C.A. Compared to the healthy group, the asymBI group achieved significantly lower FM and GM raw, scaled and motor composite scores at six and 12 months C.A., with the exception of FM raw scores at 6 months C.A. As expected, the majority of infants with asymBI did not score within the normative range for the GM
scaled scores and motor composite scores at six and 12 months C.A. These findings lend support to previous studies reporting that extremely preterm infants\textsuperscript{201}, very preterm infants\textsuperscript{202}, and infants with stroke\textsuperscript{177} achieved lower FM and GM scaled and motor composite scores on the BSID III compared to healthy, term-born infants. In the present study, most infants with asymBI scored within the normative range for FM scaled scores at six and 12 months C.A. This finding may indicate that infants with asymBI used the potentially unimpaired UL to perform FM tasks during the assessment. The majority of FM subtest items on the BSID III can be performed and assessed with one UL, which reflects a limitation of this measure when used to assess infants who are likely to have a confirmed diagnosis of UCP by 12 months C.A. The mini-Assisting Hand Assessment (mini-AHA)\textsuperscript{12} would have been more appropriate to use in the asymBI group; however, this assessment was not yet available at the commencement of this study. In contrast to an earlier study,\textsuperscript{201} two healthy, term-born infants in this study scored lower than expected based on normative BSID III data for GM scaled scores and motor composite scores at 12 months C.A. These infants may have experienced fatigue during the assessment, which would have impacted on their performance.

The BSID III has been reported to underestimate developmental delay (including FM, GM and overall motor delays) in extremely preterm (< 28 weeks GA) and term-born two-year old Australian children\textsuperscript{201}; and (ii) the Motor Scale underestimates motor impairment at four years in very preterm (< 30 weeks gestational age) two-year old Australian children.\textsuperscript{202} Compared to published BSID III normative data from the United States, only a small proportion of infants in the present study had suspected FM delay; 35% at six months C.A. and 17% at 12 months C.A. These findings lend further support to previous studies\textsuperscript{201,202}, demonstrating that the BSID III underestimates FM delay at six and 12 months C.A. in infants with clinical signs of UCP.

It must be noted that the BSID III is a discriminative rather than predictive measure of developmental delay.\textsuperscript{202} In the present study, two healthy, term-born infants in this study had suspected GM or overall motor delay at 12 months C.A. compared to BSID III normative data. This finding demonstrates that the BSID III also lacks sensitivity to discriminate between healthy, term-born infants and infants with clinical signs of UCP (four of whom were born very preterm) at six and 12 months C.A.
In the present study there were six infants who demonstrated clinical signs of UCP at six and 12 months C.A. An interesting finding was that infants with clinical signs of UCP consistently demonstrated asymmetric unimanual reaching and grasping from 14 to 18 weeks C.A. on the GRAB; and initially demonstrated less unimanual grasping compared to infants without clinical signs of UCP. This finding extends on previous work\cite{188,194}, demonstrating that the GRAB can identify asymmetries between ULs in early reach and grasp behaviours as early as 14 weeks C.A. in infants with clinical signs of UCP at six and 12 months C.A.

Based on the findings of this study, the GRAB can complement other measures for early detection of CP. These include: (i) magnetic resonance imaging (MRI) combined with a General Movements (GMs) assessment, which is currently the best available method for predicting CP (including UCP)\cite{150} and (ii) the Hand Assessment of Infants (HAI) from three to 12 months C.A.\cite{10} At present, the GRAB and the HAI are the only measures (currently under development) with potential to identify an emerging hemiparesis through evaluation of early UL motor behaviours in infants with asymBI from three to 12 months C.A.\cite{10,151} Although it is imperative to have valid and reliable measures for early detection of UCP, it is also necessary to have measures that evaluate changes in UL motor function in response to UL motor interventions. The mini-AHA (also under development) has demonstrated potential to evaluate functional hand use and efficacy of intervention in infants with clinical signs of UCP from eight to 18 months C.A.\cite{12}

Available evidence suggests that, in infants with asymBI, UCP can be accurately detected at three months C.A. using MRI combined with GMs, of which the latter evaluates asymmetries in hand and wrist movements\cite{176} and/or detects absent fidgety movements in infants with asymBI aged three months C.A.\cite{150} An emerging hemiparesis can be detected in infants with asymBI by evaluating asymmetries between ULs in: (i) early reach and grasp behaviours from 14 to 18 weeks C.A. (3.5 to 4.5 months C.A.) on the GRAB; and (ii) goal-directed unimanual and bimanual behaviours from three to 12 months C.A. on the HAI.\cite{10} The use of the impaired UL in bimanual tasks can then be evaluated in infants with clinical signs of UCP from eight to 18 months C.A.\cite{12}

Potential limitations of this study include: (i) the heterogeneity of the asymBI sample, including infants with both unilateral and asymmetric bilateral brain lesions; (ii) the relatively small sample size; (iii) limited long-term follow-up; and (iv) the
restriction of our findings to reference values on the BSID III for six and 12-month old Caucasian children. Caution must therefore be taken when interpreting our findings; and the implications of this study cannot be generalized to non-Caucasian children outside of these ages. At present, the clinical utility of the GRAB remains unclear and requires further research.

6.2.6. Conclusion

The GRAB identified that infants with asymBI demonstrated a paucity rather than asymmetry of unimanual contacts and grasps from 14 to 18 weeks C.A.; and a paucity of bimanual grasping at 18 weeks C.A. compared to healthy, term-born infants. The GRAB also identified that infants with clinical signs of UCP initially grasped less and used their unimpaired UL to demonstrate unimanual toy contacts and grasps from 14 to 18 weeks C.A., compared to infants without UCP at six months C.A. The number of unimanual contacts, grasps and bimanual grasps at 18 weeks C.A. on the GRAB were strong predictors of FM development in infants with asymBI only at six months C.A. on the BSID III. The BSID III, however, underestimated FM impairment in infants with clinical signs of UCP at six and 12 months C.A. To date, the GRAB and the HAI are the only measures with potential to identify an emerging hemiparesis based on video assessment of early unimanual and bimanual UL motor behaviours in infants with asymBI from three to 12 months C.A. The mini-AHA is the only validated measure available to evaluate the use of the impaired UL in infants with clinical signs of UCP from eight to 18 months C.A. Future research is required to: (i) evaluate the trajectory of UL motor development in infants with clinical signs of UCP using the GRAB, HAI and mini-AHA; and (ii) evaluate changes in UL motor function in response to UL motor interventions that are suitable for infants at risk of or with UCP from three to 18 months C.A.
Table 6.1. Demographic information for healthy infants and infants with asymmetric brain injury.

<table>
<thead>
<tr>
<th></th>
<th>Healthy group (n=20)</th>
<th>asymBI group (n=32)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, n (female: male)</td>
<td>9:11</td>
<td>15:17</td>
<td>1.00</td>
</tr>
<tr>
<td>Gestational age, mean (SD), wks</td>
<td>39.9 (1.1)</td>
<td>36.1 (4.9)</td>
<td>0.001*</td>
</tr>
<tr>
<td>Actual age at 6 mth assessment, mean (SD), mths</td>
<td>6.2 (0.3)</td>
<td>7.1 (1.4)</td>
<td>0.004*</td>
</tr>
<tr>
<td>Actual age at 12 mth assessment, mean (SD), mths</td>
<td>12.1 (0.4)</td>
<td>13.2 (1.3)</td>
<td>0.001*</td>
</tr>
<tr>
<td>Birthweight, mean (SD), kg</td>
<td>2.6 (1.0)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Side of brain lesion</td>
<td>-</td>
<td>n=32</td>
<td>-</td>
</tr>
<tr>
<td>Right, n (%)</td>
<td>-</td>
<td>6 (19%)</td>
<td></td>
</tr>
<tr>
<td>Left, n (%)</td>
<td>-</td>
<td>16 (50%)</td>
<td></td>
</tr>
<tr>
<td>Right &gt; Left, n (%)</td>
<td>-</td>
<td>6 (19%)</td>
<td></td>
</tr>
<tr>
<td>Left &gt; Right, n (%)</td>
<td>-</td>
<td>4 (12%)</td>
<td></td>
</tr>
<tr>
<td>Type of brain lesion</td>
<td>-</td>
<td>n=31</td>
<td>-</td>
</tr>
<tr>
<td>Stroke, n (%)</td>
<td>-</td>
<td>22 (71%)</td>
<td></td>
</tr>
<tr>
<td>IVH, n (%)</td>
<td>-</td>
<td>5 (16%)</td>
<td></td>
</tr>
<tr>
<td>PVL, n (%)</td>
<td>-</td>
<td>1 (3%)</td>
<td></td>
</tr>
<tr>
<td>Other, n (%)</td>
<td>-</td>
<td>3 (10%)</td>
<td></td>
</tr>
<tr>
<td>Maternal cultural background</td>
<td>n=12</td>
<td>n=27</td>
<td>0.17</td>
</tr>
<tr>
<td>Caucasian, n (%)</td>
<td>10 (83%)</td>
<td>25 (93%)</td>
<td></td>
</tr>
<tr>
<td>Asian, n (%)</td>
<td>2 (17%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Other, n (%)</td>
<td>0 (0%)</td>
<td>2 (7%)</td>
<td></td>
</tr>
<tr>
<td>Paternal cultural background</td>
<td>n=12</td>
<td>n=26</td>
<td>1.00</td>
</tr>
<tr>
<td>Caucasian, n (%)</td>
<td>12 (100%)</td>
<td>24 (92%)</td>
<td></td>
</tr>
<tr>
<td>Asian, n (%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Other, n (%)</td>
<td>0 (0%)</td>
<td>2 (8%)</td>
<td></td>
</tr>
<tr>
<td>Maternal education level</td>
<td>n=16</td>
<td>n=28</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>TE, n (%)</td>
<td>16 (100%)</td>
<td>9 (32%)</td>
<td></td>
</tr>
<tr>
<td>VE, n (%)</td>
<td>0 (0%)</td>
<td>8 (29%)</td>
<td></td>
</tr>
<tr>
<td>SE, n (%)</td>
<td>0 (0%)</td>
<td>9 (32%)</td>
<td></td>
</tr>
<tr>
<td>OE, n (%)</td>
<td>0 (0%)</td>
<td>2 (7%)</td>
<td></td>
</tr>
<tr>
<td>Paternal education level</td>
<td>n=15</td>
<td>n=25</td>
<td>0.001*</td>
</tr>
<tr>
<td>TE, n (%)</td>
<td>14 (93%)</td>
<td>9 (36%)</td>
<td></td>
</tr>
<tr>
<td>VE, n (%)</td>
<td>1 (7%)</td>
<td>8 (32%)</td>
<td></td>
</tr>
<tr>
<td>SE, n (%)</td>
<td>0 (0%)</td>
<td>8 (32%)</td>
<td></td>
</tr>
<tr>
<td>OE, n (%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
</tbody>
</table>

Key. asymBI, asymmetric brain injury group; wks, weeks in gestational age; mths, months in corrected age; SD, standard deviation; IVH, intraventricular haemorrhage; PVL, periventricular leukomalacia; TE, tertiary education - completed a university degree in Australia or Italy; VE, vocational education - completed a TAFE course in Australia, or professional or technical school in Italy; SE, secondary education - completed high school in Australia or Italy; OE, other education - did not complete formal education beyond primary or middle school in Australia or Italy; - unable to determine as data was only applicable or collected for one group; *, statistically significant result.
### Table 6.2.
Comparison of Grasp and Reach Assessment of Brisbane mean scores within and between groups over time using incidence rate ratios.

<table>
<thead>
<tr>
<th>Group</th>
<th>Healthy group</th>
<th>asyMBI group</th>
<th>Both groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
<td>T1: 14 wks</td>
<td>T2: 16 wks</td>
<td>T3: 18 wks</td>
</tr>
<tr>
<td></td>
<td>(n=18)</td>
<td>(n=19)</td>
<td>(n=20)</td>
</tr>
<tr>
<td>Number of unimanual contacts for each upper limb, mean (SD)</td>
<td>R</td>
<td></td>
<td></td>
</tr>
<tr>
<td>L</td>
<td>14 (11)</td>
<td>13 (14)</td>
<td>18 (15)</td>
</tr>
<tr>
<td></td>
<td>13 (15)</td>
<td>18 (14)</td>
<td>17 (12)</td>
</tr>
<tr>
<td>Difference in number of unimanual contacts between upper limbs, IRR (95% CI); p-value</td>
<td>R - L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>R - L</td>
<td>1.4 (1.1, 1.7)</td>
<td>0.001*</td>
<td>1.1 (0.9, 1.4)</td>
</tr>
<tr>
<td>U - I</td>
<td>1.2 (1.0, 1.5)</td>
<td>&lt;0.001*</td>
<td>1.3 (1.1, 1.5)</td>
</tr>
<tr>
<td>Amount of change in unimanual contacts between upper limbs and between assessment occasions, IRR (95% CI); p-value</td>
<td>R - L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>R - L</td>
<td>1.0 (0.6, 1.7)</td>
<td>0.7 (0.4, 1.2)</td>
<td>1.1 (0.6, 1.8);</td>
</tr>
<tr>
<td></td>
<td>0.94</td>
<td>0.23</td>
<td>0.80</td>
</tr>
<tr>
<td>Number of unimanual grasps for each upper limb, mean (SD)</td>
<td>L</td>
<td>R + L</td>
<td>(R + L) - (U + I)</td>
</tr>
<tr>
<td>R</td>
<td>6 (6)</td>
<td>5 (7)</td>
<td>1.0 (0.9, 1.2);</td>
</tr>
<tr>
<td>L</td>
<td>6 (6)</td>
<td>5 (6)</td>
<td>1.3 (1.7);</td>
</tr>
<tr>
<td>Difference in number of unimanual grasps between upper limbs, IRR (95% CI); p-value</td>
<td>R - L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>R - L</td>
<td>1.0 (0.6, 2.3)</td>
<td>1.6 (0.8, 3.2)</td>
<td>1.2 (0.6, 3.2);</td>
</tr>
<tr>
<td>U - I</td>
<td>0.19</td>
<td>0.69</td>
<td>0.19</td>
</tr>
<tr>
<td>Amount of change in unimanual grasps between upper limbs and between assessment occasions, IRR (95% CI); p-value</td>
<td>R - L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>R - L</td>
<td>1.2 (0.8, 1.8)</td>
<td>1.0 (0.8, 1.4)</td>
<td>1.3 (1.0, 1.6);</td>
</tr>
<tr>
<td></td>
<td>0.43</td>
<td>0.82</td>
<td>0.04*</td>
</tr>
<tr>
<td>Number of bimanual grasps for both upper limbs, mean (SD)</td>
<td>R + L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>R + L</td>
<td>2 (4)</td>
<td>3 (5)</td>
<td>7 (8)</td>
</tr>
</tbody>
</table>
Table 6.2. (continued)
Comparison of Grasp and Reach Assessment of Brisbane mean scores within and between groups over time using incidence rate ratios.

| Amount of change in bimanual grasps between groups and between assessment occasions, IRR (95% CI); p-value | (R + L) - (U + I) | T2-T1: 0.9 (0.5, 1.5); 0.63 | T3-T2: 1.2 (0.8, 1.8); 0.31 | T3-T1: 1.1 (0.7, 1.7); 0.75 |

Key. GRAB, Grasp and Reach Assessment of Brisbane; asymBI, asymmetric brain injury; IRR, incidence rate ratio; 95% CI, 95% confidence interval; SD, standard deviation; wks, weeks in corrected age (C.A.); R, right upper limb; L, left upper limb; U, potentially unimpaired upper limb; I, potentially impaired upper limb; T1, assessment occasion 1.; T2, assessment occasion 2.; T3, assessment occasion 3; *, statistically significant result.
### Table 6.3.
Comparison of Bayley Scales of Infant and Toddler Development mean scores within and between groups using mean differences.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Healthy group 6 mths (n=19)</th>
<th>12 mths (n=20)</th>
<th>Change in healthy group from 6 to 12 mths (n=20)</th>
<th>asymBI group 6 mths (n=26)</th>
<th>12 mths (n=18)</th>
<th>Change in asymBI group from 6 to 12 mths (n=18)</th>
<th>Both groups Difference between groups at 6 mths (n=45)</th>
<th>Difference between groups at 12 mths (n=38)</th>
<th>Amount of change between groups from 6 to 12 mths (n=38)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FM raw score</strong></td>
<td>21.6 (2.0)</td>
<td>30.5 (2.4)</td>
<td>8.9 (7.5,10.3)</td>
<td>20.3 (3.2)</td>
<td>28.4 (2.1)</td>
<td>8.1 (6.3,9.8)</td>
<td>1.3 (-0.4,3.0)</td>
<td>0.14</td>
<td>0.8 (-1.4,3.1)</td>
</tr>
<tr>
<td><strong>GM raw score</strong></td>
<td>26.2 (3.4)</td>
<td>42.3 (3.4)</td>
<td>16.1 (13.9,18.3)</td>
<td>22.1 (4.7)</td>
<td>34.9 (5.9)</td>
<td>12.8 (9.5,16.0)</td>
<td>4.0 (1.5,6.6)</td>
<td>0.003*</td>
<td>3.3 (-0.6,7.3)</td>
</tr>
<tr>
<td><strong>FM scaled score</strong></td>
<td>12.4 (2.2)</td>
<td>12.3 (2.6)</td>
<td>-0.1 (-1.6, 1.5)</td>
<td>9.9 (3.2)</td>
<td>9.4 (2.0)</td>
<td>-0.5 (-2.2,1.3)</td>
<td>2.4 (0.7,4.2)</td>
<td>0.01*</td>
<td>2.9 (1.3,4.4)</td>
</tr>
<tr>
<td><strong>GM scaled score</strong></td>
<td>11.8 (3.1)</td>
<td>11.2 (3.7)</td>
<td>-0.6 (-2.9, 1.6)</td>
<td>7.0 (2.5)</td>
<td>5.4 (3.0)</td>
<td>-1.6 (-3.3,0.1)</td>
<td>4.8 (3.1,6.5)</td>
<td>&lt;0.001*</td>
<td>5.7 (3.5,7.9)</td>
</tr>
<tr>
<td><strong>Motor scale composite score</strong></td>
<td>112.7 (13.9)</td>
<td>110.7 (16.7)</td>
<td>-2.0 (-12.0, 8.0)</td>
<td>90.9 (15.3)</td>
<td>84.7 (13.1)</td>
<td>-6.2 (-15.2,2.7)</td>
<td>21.8 (12.8,30.8)</td>
<td>&lt;0.001*</td>
<td>26.0 (16.1,36.0)</td>
</tr>
</tbody>
</table>

**Key.** BSID III; Bayley Scales of Infant and Toddler Development (version three); asymBI, asymmetric brain injury; mean difference; SD, standard deviation; 95% CI, 95% confidence interval; MD, mean difference; mths, months in corrected age (C.A.); FM, fine motor; GM, gross motor; *, statistically significant result.
Table 6.4. Association between Grasp and Reach Assessment of Brisbane mean scores and Bayley Scales of Infant and Toddler Development mean scores within and between groups over time using regression coefficients.

<table>
<thead>
<tr>
<th>Variable</th>
<th>6 mths (n=19)</th>
<th>12 mths (n=20)</th>
<th>6 mths (n=26)</th>
<th>12 mths (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>UNIMANUAL CONTACTS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amount of change in FM raw scores for every increase of one unimanual contact using each upper limb, r (95% CI); p-value</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R</td>
<td>0.01 (-0.1, 0.1);</td>
<td>-0.01 (-0.1, 0.1);</td>
<td>U</td>
<td>0.1 (-0.04, 0.2); 0.1 (-0.02, 0.69)</td>
</tr>
<tr>
<td>L</td>
<td>0.81</td>
<td>0.40</td>
<td>I</td>
<td>0.1 (-0.02, 0.2); 0.1 (-0.01, 0.03)</td>
</tr>
<tr>
<td>Amount of change in GM raw scores for every increase of one unimanual contact using each upper limb, r (95% CI); p-value</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R</td>
<td>0.02 (-0.1, 0.1);</td>
<td>0.02 (-0.02, 0.2);</td>
<td>U</td>
<td>0.1 (-0.2, 0.01); 0.1 (-0.4, 0.1);</td>
</tr>
<tr>
<td>L</td>
<td>0.1 (0.01, 0.3);</td>
<td>0.14 (0.02, 0.3);</td>
<td>I</td>
<td>0.02 (-0.02, 0.4); 0.1 (-0.04, 0.2);</td>
</tr>
<tr>
<td>Amount of change in FM scaled scores for every increase of one unimanual contact using each upper limb, r (95% CI); p-value</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R</td>
<td>0.02 (-0.1, 0.1);</td>
<td>-0.01 (-0.1, 0.1);</td>
<td>U</td>
<td>0.1 (-0.02, 0.2); 0.1 (-0.02, 0.17)</td>
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<tr>
<td>L</td>
<td>0.56</td>
<td>0.79</td>
<td>I</td>
<td>0.2 (0.1, 0.3); 0.1 (-0.003, 0.04)</td>
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<tr>
<td>Amount of change in GM scaled scores for every increase of one unimanual contact using each upper limb, r (95% CI); p-value</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>R</td>
<td>0.1 (0.02, 0.2);</td>
<td>0.1 (-0.03, 0.2);</td>
<td>U</td>
<td>0.1 (-0.02, 0.1); 0.1 (-0.2, 0.1);</td>
</tr>
<tr>
<td>L</td>
<td>0.1 (0.03, 0.3);</td>
<td>0.1 (-0.02, 0.3);</td>
<td>I</td>
<td>0.04 (-0.05, 0.06); 0.1 (-0.2, 0.1);</td>
</tr>
<tr>
<td>Amount of change in motor composite scores for every increase of one unimanual contact using each upper limb, r (95% CI); p-value</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R</td>
<td>0.4 (-0.03, 0.8);</td>
<td>0.2 (-0.4, 0.7);</td>
<td>U</td>
<td>0.5 (0.04, 1.0); 0.1 (-0.6, 0.97)</td>
</tr>
<tr>
<td>L</td>
<td>0.5 (-0.03, 1.0);</td>
<td>0.2 (-0.5, 0.9);</td>
<td>I</td>
<td>0.6 (0.1, 1.1); 0.2 (-0.4, 0.9);</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variable</th>
<th>6 mths (n=19)</th>
<th>12 mths (n=20)</th>
<th>6 mths (n=26)</th>
<th>12 mths (n=18)</th>
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<td><strong>UNIMANUAL GRASPS</strong></td>
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</tr>
<tr>
<td>Amount of change in FM raw scores for every increase of one unimanual grasp using each upper limb, r (95% CI); p-value</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R</td>
<td>0.03 (-0.1, 0.1);</td>
<td>0.04 (-0.1, 0.2);</td>
<td>U</td>
<td>0.1 (-0.1, 0.3); 0.04 (-0.1, 0.04)</td>
</tr>
<tr>
<td>L</td>
<td>0.1 (-0.1, 0.2);</td>
<td>-0.04 (-0.2, 0.1);</td>
<td>I</td>
<td>0.2 (0.1, 0.4); 0.1 (-0.03, 0.01)</td>
</tr>
<tr>
<td>Amount of change in GM raw scores for every increase of one unimanual grasp using each upper limb, r (95% CI); p-value</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R</td>
<td>0.2 (-0.1, 0.4);</td>
<td>0.3 (0.1, 0.4);</td>
<td>U</td>
<td>0.1 (-0.3, 0.4), 0.01 (-0.3, 0.3)</td>
</tr>
<tr>
<td>L</td>
<td>0.21</td>
<td>0.04*</td>
<td>I</td>
<td>0.1 (-0.2, 0.4); 0.04 (-0.5, 0.4);</td>
</tr>
<tr>
<td>Amount of change in FM scaled scores for every increase of one unimanual grasp using each upper limb, r (95% CI); p-value</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R</td>
<td>0.04 (-0.1, 0.2);</td>
<td>0.1 (-0.1, 0.1);</td>
<td>U</td>
<td>0.2 (0.01, 0.3); 0.05 (-0.1, 0.1)</td>
</tr>
<tr>
<td>L</td>
<td>0.1 (-0.1, 0.2);</td>
<td>-0.04 (-0.2, 0.1);</td>
<td>I</td>
<td>0.3 (0.1, 0.4); 0.1 (-0.1, 0.2);</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variable</th>
<th>6 mths (n=19)</th>
<th>12 mths (n=20)</th>
<th>6 mths (n=26)</th>
<th>12 mths (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BIMANUAL GRASPS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amount of change in FM raw scores for every increase of one bimanual grasp using both upper limbs, r (95% CI); p-value</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R + L</td>
<td>0.1 (-0.1, 0.2);</td>
<td>0.03 (-0.1, 0.2);</td>
<td>U + I</td>
<td>0.2 (0.1, 0.4); 0.1 (-0.03, 0.01)</td>
</tr>
<tr>
<td>Amount of change in GM scaled scores for every increase of one bimanual grasp using both upper limbs, r (95% CI); p-value</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R + L</td>
<td>0.1 (-0.1, 0.4);</td>
<td>0.2 (0.02, 0.5);</td>
<td>U + I</td>
<td>0.1 (-0.1, 0.4); 0.1 (-0.3, 0.5);</td>
</tr>
</tbody>
</table>

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Table 6.4. (continued)
Association between Grasp and Reach Assessment of Brisbane mean scores and Bayley Scales of Infant and Toddler Development mean scores within and between groups over time using regression coefficients.

<table>
<thead>
<tr>
<th></th>
<th>Amount of change in FM scaled scores for every increase of one bimanual grasp using both upper limbs, r (95% CI); p-value</th>
<th>Amount of change in GM scaled scores for every increase of one bimanual grasp using both upper limbs, r (95% CI); p-value</th>
<th>Amount of change in motor composite scores for every increase of one bimanual grasp using both upper limbs, r (95% CI); p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R + L</td>
<td>U + I</td>
<td>R + L</td>
</tr>
<tr>
<td></td>
<td>0.1 (-0.1, 0.2); 0.31</td>
<td>0.3 (0.1, 0.4); 0.001*</td>
<td>0.6 (-0.2, 1.5); 0.012*</td>
</tr>
<tr>
<td></td>
<td>0.01 (-0.2, 0.2); 0.86</td>
<td>0.1 (-0.5, 0.2); 0.19</td>
<td>0.3 (-0.8, 1.4); 0.53</td>
</tr>
<tr>
<td></td>
<td>0.2 (0.1, 0.4); 0.86</td>
<td>0.2 (0.03, 0.3); 0.02*</td>
<td>0.2 (0.03, 0.3); 0.04*</td>
</tr>
<tr>
<td></td>
<td>0.1 (-0.1, 0.4); 0.24</td>
<td>0.04 (-0.2, 0.2); 0.02*</td>
<td>0.04 (-0.5, 1.3); 0.36</td>
</tr>
</tbody>
</table>

Key. GRAB, Grasp and Reach Assessment of Brisbane; BSID III, Bayley Scales of Infant and Toddler Development (version three); asymBI, asymmetric brain injury; mths, months in corrected age; 95% CI, 95% confidence interval; SD, standard deviation; FM, fine motor; GM, gross motor; R, right upper limb; L, left upper limb; U, potentially unimpaired upper limb; I, potentially impaired upper limb; r, regression coefficient; *, statistically significant result.
Figure 6.1. Mean number ± standard deviation of unimanual contacts for the right and left upper limbs in the healthy group (6.1.A.); mean number ± standard deviation of unimanual grasps for the right and left upper limbs in the healthy group (6.1.B.); mean number ± standard deviation of unimanual contacts for the potentially unimpaired and impaired upper limbs in the asymmetric brain injury group (6.1.C.); mean number ± standard deviation of unimanual grasps for the potentially unimpaired and impaired upper limbs in the asymmetric brain injury group (6.1.D.) at 14, 16 and 18 weeks corrected age on the Grasp and Reach Assessment of Brisbane.
Figure 6.2. Mean number and standard deviation of bimanual grasps for each group at 14, 16 and 18 weeks corrected age on the Grasp and Reach Assessment of Brisbane.

Key. asymBI, asymmetric brain injury group.
6.3.A. Fine Motor subtest scaled scores at 6 and 12 months corrected age

6.3.B. Gross Motor subtest scaled scores at 6 and 12 months corrected age

Figure 6.3. Scatter plot of scaled scores on the fine motor subtest (with mean and standard deviation) for each group (6.3.A.); and composite scores on the motor scale (with mean and standard deviation) for each group (6.3.B.) at six and 12 months corrected age on the Bayley Scales of Infant and Toddler Development (version three). Continuous line indicates mean reference score; dashed line indicates cut-off score for classification of suspected delay.

Key. asymBI, asymmetric brain injury group.
Appendix 6.A. Mean number and standard deviation of unimanual contacts (6.A.1.) and of unimanual grasps (6.A.2.) for each upper limb in infants with asymmetric brain injury with and without clinical signs of unilateral cerebral palsy at 14, 16 and 18 weeks corrected age on the Grasp and Reach Assessment of Brisbane.

**Key.** UCP, with clinical signs of unilateral cerebral palsy; No UCP, no clinical signs of unilateral cerebral palsy.
Appendix 6.B.
Comparison of Grasp and Reach Assessment of Brisbane mean scores within and between infants with and without clinical signs of unilateral cerebral palsy over time using incidence rate ratios.

<table>
<thead>
<tr>
<th>Group</th>
<th>Infants without clinical signs of UCP at six months sub-group</th>
<th>Infants with clinical signs of UCP at six months sub-group</th>
<th>Both sub-groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
<td>T1: 14 wks (n=15)</td>
<td>T2: 16 wks (n=14)</td>
<td>T3: 18 wks (n=15)</td>
</tr>
<tr>
<td>Number of unimanual contacts for each upper limb, mean (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>U</td>
<td>13 (15)</td>
<td>18 (16)</td>
<td>20 (14)</td>
</tr>
<tr>
<td>I</td>
<td>14 (15)</td>
<td>20 (16)</td>
<td>19 (11)</td>
</tr>
<tr>
<td>Difference in number of unimanual contacts between upper limbs, IRR (95% CI); p-value</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>U - I</td>
<td>1.1 (0.9, 1.3); 0.39</td>
<td>1.0 (0.8, 1.1); 0.23</td>
<td>0.9 (0.8, 1.1); 0.34</td>
</tr>
<tr>
<td>Number of unimanual grasps for each upper limb, mean (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>U</td>
<td>4 (6)</td>
<td>6 (8)</td>
<td>11 (10)</td>
</tr>
<tr>
<td>I</td>
<td>6 (8)</td>
<td>10 (12)</td>
<td>10 (8)</td>
</tr>
<tr>
<td>Difference in number of unimanual grasps between upper limbs, IRR (95% CI); p-value</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>U - I</td>
<td>1.3 (0.9, 1.8); 0.10</td>
<td>1.6 (1.2, 2.0); 0.001*</td>
<td>1.0 (0.8, 1.2); 0.66</td>
</tr>
</tbody>
</table>

Key. GRAB, Grasp and Reach Assessment of Brisbane; asymBI, asymmetric brain injury; UCP, unilateral cerebral palsy; IRR, incidence rate ratio; 95% CI, 95% confidence interval; SD, standard deviation; wks, weeks in corrected age (C.A.); R, right upper limb; L, left upper limb; U, potentially unimpaired upper limb; I, potentially impaired upper limb; T1, assessment occasion 1.; T2; assessment occasion 2.; T3, assessment occasion 3; *, statistically significant result.
6.3. Summary and conclusions

Key findings of this paper were:

- Infants with asymBI demonstrated a paucity rather than asymmetry in unimanual reach and grasp behaviours from 14 to 18 weeks C.A.; and a paucity of bimanual grasping at 18 weeks C.A. compared to healthy, term-born infants on the GRAB.

- Infants with asymBI demonstrated asymmetric unimanual reach and grasp behaviours from 14 to 18 weeks C.A.; and a paucity of unimanual grasping at 14 weeks C.A. on the GRAB.

- Although infants with asymBI scored significantly lower on the BSID III motor scale compared to healthy, term-born infants; the BSID III underestimated FM impairment in infants with clinical signs of UCP at six months C.A.

- The number of unimanual contacts, grasps and bimanual grasps at 18 weeks C.A. on the GRAB were strong predictors of FM, GM and overall motor performance only at 6 months C.A. on the BSID III for infants with asymBI.

This chapter addressed Aim 4 by presenting the final measurement paper on the GRAB, which examined and reported longitudinal development of reach to grasp in infants with asymBI and healthy infants at 14, 16 and 18 weeks C.A. on the GRAB. As predicted in Hypothesis 4, this study demonstrated that the GRAB identified differences in early unimanual and bimanual reach to grasp development from 14 to 18 weeks C.A. between infants with asymBI compared to healthy infants. Furthermore, this study also demonstrated that behavioural events (i.e. number of unimanual contacts, grasps and bimanual grasps) measured on the GRAB, could predict delayed motor development in infants with asymBI compared to healthy infants at 6 months C.A. on the BSID III. An important finding of this study was that the GRAB also identified asymmetries between ULs in early unimanual and bimanual reach and grasp behaviours at 14, 16 and 18 weeks C.A. in infants with asymBI. The next and final chapter of this thesis is comprised of the grand discussion of findings and conclusions from the doctoral program.
Chapter 7: Grand Discussion and conclusions

7.1. Introduction

The final chapter of this thesis summarises the main findings of each component of the doctoral program according to the hypotheses that were outlined in Chapter 1. The findings will be discussed in the context of available evidence supporting early UL motor interventions and measures of UL motor function for infants with asymBI. The strengths and limitations of this research will then be highlighted. Following this, considerations for future research and clinical implications of this research will be presented.

7.2. Overview of findings (per Hypothesis/Chapter)

This doctoral program has identified that there is limited evidence supporting the efficacy of non-operative UL motor interventions in infants with asymBI, who are at risk of UCP (Hypothesis 1, Chapter 2). Another important finding of this research is the limited evidence for valid and reliable measures to accurately detect UCP and to quantify early abnormalities in UL motor development to predict UCP in this young and at-risk population. This finding provided the rationale for: (i) developing a new research measure called the Grasp and Reach Assessment of Brisbane (GRAB); (ii) evaluating its construct validity and internal consistency (Hypothesis 2, Chapter 4); (iii) intra- and inter-rater reproducibility (i.e. reliability and agreement; Hypothesis 3, Chapter 5); and (iv) predictive validity (Hypothesis 4, Chapter 6).

7.2.1. Hypothesis 1.

There will be limited evidence reporting the efficacy of early UL motor interventions for infants younger than three years with asymBI in improving UL motor function outcomes, compared with usual care.

The evidence base reporting the efficacy of UL motor interventions for school-aged children with CP (including UCP) indicates that there is moderate to strong evidence for activity-based, goal-directed UL interventions such as signature CIMT, mCIMT, hybrid CIMT, FUT and OT supplemented with intramuscular UL injections of BoNT-A to improve UL motor function.13,106 There remains, however, a paucity of evidence to support the efficacy of infant-friendly UL motor interventions for infants with asymBI, who are at risk of UCP by 12 months of age.203
The book chapter\textsuperscript{60} (Chapter 1) identified three early interventions that are promising for infants with asymBI: bilateral stimulation of hand function\textsuperscript{204}, mCIMT\textsuperscript{5} and AOT.\textsuperscript{58,76} The potential impact of these three interventions remains unclear, however, and requires further investigation.\textsuperscript{60} The systematic review\textsuperscript{203} (Chapter 2) identified that signature CIMT, mCIMT, hybrid CIMT, FUT and OT supplemented with intramuscular UL injections of BoNT-A are more effective than usual care in improving unimanual and bimanual UL function in school-aged children (including infants) with UCP.\textsuperscript{203} There was limited use, however, of valid and reliable outcome measures to quantify meaningful change in response to interventions in infants with or at risk of UCP.\textsuperscript{203} Prior to referral to interventions, accurate detection of infants who are at risk of UCP needs to occur.\textsuperscript{58,60,175} It was identified from available literature that infants at risk of UCP demonstrate: (i) asymmetries between hands in wrist movements during the fidgety period\textsuperscript{176}; (ii) laterality between ULs in reaching\textsuperscript{178}; and (iii) less bimanual manipulation\textsuperscript{177} compared to healthy infants. There was limited use, however, of valid and reliable measures of UL asymmetries in reach and grasp behaviours for early detection of infants who are likely to demonstrate clinical signs of UCP by 12 months of age. To contribute to this gap in the evidence base of valid and reliable measures for early detection of UCP in infants with asymBI, this doctoral program sought to develop, evaluate and report a new measure called the Grasp and Reach Assessment of Brisbane (GRAB). This contribution of research on the GRAB is addressed in Hypotheses 2, 3 and 4.

7.2.2. Hypothesis 2.

The GRAB will demonstrate evidence of strong construct validity and internal consistency as a quantitative measure for: (i) detecting asymmetries between ULs in reach and grasp behaviours in infants with asymBI; and (ii) identifying differences in reach and grasp behaviours between healthy infants and infants with asymBI.

Findings of the validity study\textsuperscript{188} (Chapter 4) suggest that the GRAB demonstrated evidence of moderate to strong construct validity. Firstly, infants with asymBI only demonstrated asymmetry between ULs for unimanual grasps. Secondly, infants with asymBI demonstrated asymmetry between ULs for only 20\% more of the time for unimanual contacts; and a paucity of bimanual grasps compared to healthy infants. The GRAB demonstrated evidence of strong internal consistency for both the Time Phase (TP) and Toy Colour Phase (TCP) items of the GRAB for a
majority of unimanual reach and grasp behaviours only, which were: (i) number of
unimanual contacts; (ii) number of unimanual grasps; (iii) duration of no unimanual
activity; (iv) duration of prehensile movements; and (v) duration of transport phase.
The GRAB demonstrated evidence of weak internal consistency for both TP and
TCP items of the GRAB for: (i) duration of unimanual contribution to hands at
midline; and (ii) duration of bimanual midline behaviour. The GRAB detected and
quantified the presence, absence or asymmetry between ULs of several early reach
and grasp behaviours both in infants with asymBI and healthy infants at 18 weeks
C.A. The next step was to evaluate intra- and inter-rater reproducibility (i.e. reliability
and agreement) of the measurements on the GRAB; which is addressed in
Hypothesis 3.

7.2.3. Hypothesis 3.

The GRAB will demonstrate evidence of strong intra- and inter-rater reliability and
high percentage intra- and inter-rater agreement of measurements.

Findings of the reproducibility study\textsuperscript{194} (Chapter 5) suggest that the GRAB
demonstrated evidence of strong intra-rater reliability for both behavioural events
(i.e. the number of unimanual contacts, grasps and bimanual grasps); and strong
intra- and inter-rater reliability for behavioural duration (i.e. the duration of unimanual
grasps, unimanual contribution to hands at midline, bimanual grasps and bimanual
midline behaviour). The GRAB demonstrated evidence of high percentage intra- and
inter-rater agreement ($\geq 90\%$) for behavioural events only (i.e. the number of
unimanual and bimanual grasps); and high percentage intra-rater agreement ($\geq
90\%$) for the number of unimanual contacts. An important finding of the
reproducibility study was that behavioural events were more reliable and consistently
measured compared to behavioural duration on the GRAB. Behavioural events were
therefore selected for further evaluation in the next study – evaluation of the
longitudinal development of reach to grasp on the GRAB and prediction of FM
development on the BSID III Motor Scale. The longitudinal study was performed to
address Hypothesis 4.
7.2.4. Hypothesis 4.

Differences in the longitudinal development of reach and grasp behaviours between healthy infants and infants with asymBI at 14, 16 and 18 weeks C.A. on the GRAB, as well as differences between ULs in infants with asymBI at 14, 16 and 18 weeks C.A. on the GRAB will predict delayed motor development at six and 12 months C.A. on the BSID III in infants with asymBI compared to healthy infants.

The longitudinal study\textsuperscript{205} (Chapter 6) identified that infants with asymBI demonstrated a paucity rather than asymmetry of unimanual contacts and grasps from 14 to 18 weeks C.A on the GRAB; a paucity of bimanual grasps at 18 weeks C.A. on the GRAB; and scored lower on the BSID III Motor Scale at six and 12 months C.A. compared to healthy infants. Preliminary findings suggest that the number of unimanual contacts, grasps and bimanual grasps at 18 weeks C.A. on the GRAB are strong predictors of FM development on the BSID III Motor Scale for infants with asymBI at six months C.A. The GRAB detected asymmetries in unimanual contacts and grasps; and a paucity of unimanual grasps from 14 to 18 weeks C.A. in infants with clinical signs of hemiplegia compared to those without at six months C.A. Findings of the longitudinal study suggest that the GRAB demonstrated evidence of moderate to strong predictive validity. The longitudinal study also identified that the BSID III underestimated FM impairment in infants with clinical signs of hemiplegia at six months C.A. This finding provides further support to previous studies which have reported that the BSID III underestimates motor delay in at-risk children.\textsuperscript{201,202}

7.3. Contextualising findings

Findings from the book chapter\textsuperscript{58} (Chapter 1) and the systematic review\textsuperscript{203} (Chapter 2) confirm that the evidence base supporting the efficacy of infant-friendly UL motor interventions for infants with or at risk of UCP is limited. This doctoral program also identified that there is limited use of valid and reliable measures to examine efficacy of interventions and to quantify meaningful changes in UL motor function in response to interventions in at-risk infants. Furthermore, in recent literature comparing the development of UL behaviours between infants with stroke and healthy infants,\textsuperscript{177,178} there was also limited use of valid and reliable measures for early detection and/or prediction of UCP in at-risk infants by 12 months of age. To contribute to this gap in the evidence base for early detection/prediction of UCP in
infants with asymBI, this doctoral program sought to develop, evaluate and report on a new measure called the GRAB. Findings from the validity, reproducibility and longitudinal studies on the GRAB have provided the first evidence for a new research measure to detect, quantify and evaluate emerging development of reach to grasp of both upper limbs in infants with asymBI and healthy infants who are younger than six months C.A. The key findings are discussed below in the context of available evidence for: (i) the efficacy of UL motor interventions that are suitable for infants with asymBI; and (ii) early detection and/or prediction of UCP in infants with asymBI who are younger than 12 months C.A.

7.3.1. Evidence supporting the efficacy of early upper limb motor interventions

There is a paucity of evidence supporting the efficacy of UL motor interventions in infants with asymBI. The book chapter\textsuperscript{58} in Chapter 1 identified three early interventions that are promising for infants with asymBI: bilateral stimulation of hand function,\textsuperscript{204} mCIMT\textsuperscript{5} and AOT.\textsuperscript{58,76} The potential impact of these interventions on the development of corticospinal tracts following a brain lesion and development of early UL motor function remain unclear, however, and require further investigation.\textsuperscript{60} The systematic review\textsuperscript{203} in Chapter 2 identified only one published RCT with a study sample of participants with UCP who were all younger than three years.\textsuperscript{5} The RCT reported that an ecological approach of CIMT (eco-CIMT) was more effective than usual care when eco-CIMT was delivered by parents and preschool teachers (who were supervised by an occupational therapist).\textsuperscript{5} Furthermore, a recently published systematic review reported that early EE provides small positive effects on motor outcomes in infants with or at risk of CP (including UCP).\textsuperscript{6} Employing an ecological approach to intervention can enhance functional outcomes in infants\textsuperscript{206}, including those with or at risk of UCP.

Based on an effect size analysis of interventions in RCTs of school-aged children that included infants with UCP, the systematic review in Chapter 2 identified that mCIMT, hybrid CIMT and OT supplemented with intramuscular UL injections of BoNT-A are more effective than usual care in improving unimanual and bimanual UL function.\textsuperscript{203} One key element of an effective CIMT program for infants with asymBI may be applying and/or integrating the principles of motor learning theory and ecological theory in the program. Another key element of an effective CIMT program for infants with asymBI may be goal-directed unimanual and bimanual training.
delivered one-on-one by a therapist as well as within a group setting. Another key element of an effective CIMT program for infants with asymBI may be intensive practice delivered within the home environment, with or without additional practice in another environment. The key elements of a program consisting of OT supplemented with intramuscular UL BoNT-A injections may be goal-directed training followed by a home program, rather than higher doses of intramuscular UL BoNT-A injections for young children between two and three years (as BoNT-A is not licensed for use in infants younger than two years). More recent RCTs of infant-friendly interventions are currently in progress which will evaluate the efficacy of baby-CIMT and AOT in infants with asymBI who are younger than 12 months C.A.

The major gap in current evidence identified in the systematic review was that there is limited use of valid and reliable outcome measures to quantify meaningful change in response to interventions in this young and at-risk population. After referral to interventions within the critical period of brain development, meaningful change in UL motor function (i.e. improved UL reach and grasp and eventual bimanual manipulation) following intervention needs to be examined using valid and reliable measures of UL motor function. The mini-AHA is currently the only available and validated measure to evaluate the use of the impaired UL during bimanual performance in infants with confirmed UCP aged eight to 18 months. There is no validated and published measure at present which examines the efficacy of interventions and quantifies meaningful change in UL motor function following intervention in infants with asymBI who are at risk of UCP, prior to eight months.

7.3.2. Evidence supporting the measurement of early upper limb motor development for early detection and/or prediction of unilateral cerebral palsy and changes in upper limb motor function in response to intervention

Accurate detection of infants who are at risk of UCP needs to occur prior to infants being referred to UL motor interventions within the critical period of brain development. This doctoral program highlights the need for valid and reliable UL motor function measures to enable earlier detection of infants who are likely to demonstrate clinical signs of UCP by 12 months of age. To date, UCP has been identified in infants with perinatal or neonatal stroke using: (i) asymmetries of wrist movements during the fidgety period (nine to 20 weeks post-term) of GMs; (ii)
measurement of bimanual midline toy manipulation (two to seven months post-term); and (iii) measurement of reaching trajectories (two to seven months post-term). There is no validated and published measure at present which quantifies asymmetries of early UL reach to grasp development in infants with asymBI prior to six months C.A. for earlier detection of UCP. This doctoral program contributes to the limited evidence of early detection in this very young and at-risk population by developing, evaluating and reporting the first evidence of psychometric properties (i.e. construct validity, internal consistency, intra- and inter-rater reproducibility and predictive validity) of a new measure called the Grasp and Reach Assessment of Brisbane (GRAB).

Another measure to quantify asymmetries of early UL behaviours in infants from three to 12 months C.A. called the Hand Assessment of Infants (HAI) has since been reported; and it is currently under development, with psychometric properties not yet published. The HAI aims to evaluate asymmetries between ULs in goal-directed unimanual and bimanual UL actions in infants with asymBI aged three to 12 months; while the GRAB aims to evaluate asymmetries between ULs in early reach and grasp behaviours in infants with asymBI aged 14 to 18 weeks C.A. A previously published study identified that asymmetries in wrist movements at fidgety age on the GMs can indicate an emerging hemiparesis in infants with neonatal stroke prior to six months C.A. Findings of this doctoral program extend on this earlier work by identifying: (i) asymmetries between ULs in early unimanual reach and grasp behaviours in infants with asymBI at 14, 16 and 18 weeks C.A. on the GRAB; and (ii) that behavioural events (i.e. number of unimanual contacts, grasps and bimanual grasps) at 18 weeks C.A. are strong predictors of FM development in infants with asymBI at six months C.A. on the BSID III Motor Scale. Two previously published studies have identified laterality between ULs in reaching and less frequent bimanual manipulation in infants with stroke compared to healthy infants aged two to seven months C.A. Findings of this doctoral program both confirm and extend on this earlier work by identifying: (i) asymmetries between ULs in unimanual contacts at 14 weeks C.A. and unimanual grasps at 18 weeks C.A. in infants with asymBI; and (ii) a paucity of bimanual grasps in infants with asymBI compared to healthy infants at 18 weeks C.A. on the GRAB. To date, the GRAB and the HAI are the only measures that can potentially identify infants who are at risk of UCP prior to six months C.A.
The GRAB has potential to complement existing measures to detect and/or evaluate UL asymmetries in infants at risk of UCP as it can be performed: (i) two weeks after a GMs assessment at three months C.A.; (ii) at the same time as a HAI assessment at three months C.A.; and (iii) five months prior to a mini-AHA. Furthermore, this doctoral program identified that behavioural events (i.e. number of unimanual contacts, grasps and bimanual grasps) at 18 weeks C.A. on the GRAB are strong predictors of FM development in infants with asymBI at six months C.A. on the BSID III Motor Scale. The BSID III, however, has previously been reported to underestimate motor delay in extremely preterm and term-born two-year old Australian children and motor impairment in very preterm-born two-year old Australian children. Findings of this doctoral program provide further support to this earlier work by identifying that the BSID III Motor Scale underestimates FM delay at six and 12 months C.A. in Australian and Italian infants with clinical signs of UCP. The BSID III lacks sensitivity to discriminate between infants at risk of UCP and healthy infants at six and 12 months C.A for FM development. Furthermore, FM scaled scores may not accurately reflect FM development in infants with asymBI as the majority of FM subtest items can be performed using one UL. This doctoral program highlights the need for valid and reliable measures (such as the GRAB and the HAI) to detect UCP in at-risk infants earlier, by quantifying asymmetric development of reach to grasp. An important finding of this research on the GRAB is that a paucity and/or asymmetric development of reach to grasp may be a strong clinical sign of hemiplegia.

The GRAB is a research measure, rather than a clinical tool, that utilises a structured behavioural coding approach to quantify emerging reach and grasp behaviours in very young infants. Behavioural coding is commonly utilised in infant studies to monitor and quantify behaviours of interest, such as upper limb reaching (e.g.,). The GRAB was developed to address a gap in the literature to quantify and evaluate the symmetry of emerging reach and grasp behaviours between ULs in very young infants with asymBI compared to typically developing infants. Similarly to the behavioural coding utilised in earlier infant studies (e.g.,), the GRAB quantifies the number and duration of toy contacts. The GRAB, however, was designed specifically for this research and for this very young population. The GRAB involved consultation with an expert panel, training of assessors, and its scoring criteria and procedure underwent an iterative process and
several revisions until a standardised criteria and procedure were established. Field testing and reproducibility testing were also undertaken on the GRAB. In addition, the GRAB utilised standardised toys and toy presentations, scoring criteria and procedure are standardised. Furthermore, the structured behavioural coding utilised in the GRAB extends on earlier work (e.g. 109, 177, 178) by providing categorisation of early UL behaviours and quantification of behaviours in terms of frequency, duration, and degree of asymmetry between ULs.

7.4. Strengths and limitations of the research

7.4.1. Strengths

This doctoral program provides the first evidence of the development, evaluation and reporting of a new research measure to quantify the early development of reach to grasp in infants with asymBI and healthy infants at 14, 16 and 18 weeks C.A.

Identification of gap in evidence base for validated measures

This doctoral program identified that there is a paucity of valid and reliable measures for: (i) early detection and/or prediction of UCP; and (ii) examining efficacy of interventions and quantifying meaningful change in response to interventions in this very young and at-risk population. To the author’s knowledge, the GRAB and the HAI are the only measures that can potentially detect UCP in infants with asymBI by quantifying and evaluating early asymmetries in UL behaviours in infants with asymBI who are younger than six months C.A. The development of the GRAB and reporting of its psychometric properties contributes to the gap in the evidence base of valid and reliable UL measures for infants with asymBI. Prior to this doctoral program, asymmetries in wrist movements during fidgety age (12 weeks C.A.) in a GMs assessment was the only validated and published measure to predict UCP in infants with neonatal stroke. Sensitivity of the global assessment of GMs in the fidgety period was moderate (0.75; 95%CI 36-96); and specificity was excellent (100; 95%CI 46-100). Infants with clinical signs of hemiplegia demonstrated significantly more asymmetries in wrist movements compared to infants without clinical signs of hemiplegia (MD=0.68, 95%CI 0.20-1.16, \( p=0.006 \)) and healthy infants (MD=0.70, 95%CI 0.26-1.15, \( p < 0.001 \)). Although asymmetries in early UL behaviours have been described as a potential indicator of UCP in infants with neonatal or perinatal stroke, no valid and reliable measure of UL asymmetries has been published.
In infants with confirmed UCP aged eight to 18 months, the mini-AHA can be used to evaluate the use of the impaired UL during bimanual performance. To date, the mini-AHA is the only validated and published measure that can quantify and evaluate meaningful change in UL motor function following interventions in infants with UCP. The current utility of the GRAB is that it is more suitable for research settings. The clinical utility of the HAI is not yet known. There is no validated and published measure at present which examines the efficacy of interventions and quantifies meaningful change in UL motor function following interventions in infants with asymBI who are at risk of UCP, prior to eight months C.A.

**Iterative process of development and novel data**

The development of the GRAB involved an iterative process which included several stages of testing and evaluation. In the validity study, the GRAB demonstrated evidence of strong internal consistency for the number of unimanual contacts and grasps (behavioural events); and weak internal consistency for the duration of unimanual contribution to hands at midline and bimanual midline behaviour (behavioural duration). These findings suggest that behavioural events are more consistent, compared to behavioural duration. In the reproducibility study, the GRAB demonstrated evidence of strong reliability and high percentage agreement (≥ 90%) for the number of unimanual and bimanual grasps (behavioural events). This finding suggests that behavioural events are more reliably and consistently measured on the GRAB, compared to behavioural duration. In light of these key findings from the reproducibility paper, behavioural events were utilised in the analysis of predictive validity of the GRAB in the longitudinal study. The number of contacts and grasps were also considered to be potentially more useful as indicators of an infant’s attempt to contact or grasp a toy with success compared to duration of time (as a prolonged grasp, for instance, could have been due to difficulties with release after grasp).

**Evaluation of reproducibility**

Reliability is commonly used in measurement studies to determine the consistency of measurements using the ICC. The ICC, however, is influenced by the heterogeneity of the sample population studies and is not sufficient to represent consistency of repeated measurements. Reproducibility testing of the GRAB involved evaluation of both reliability and agreement, which enabled evaluation of the consistency of measurements, as well as the degree of similarity between
repeated measurements.\textsuperscript{190-192} The GRAB demonstrated evidence of strong reliability and high percentage agreement (≥ 90\%) for the number and duration of unimanual and bimanual grasps (behavioural events and duration); and weak reliability and low percentage agreement (< 90\%) for the duration of no unimanual activity and other unimanual activity.\textsuperscript{194} These findings suggest that: (i) unimanual and bimanual grasping are the most reliable and consistently measured early reach and grasp behaviours; and (ii) no unimanual activity and other unimanual activity are the least reliable and least consistently measured behaviours on the GRAB.

**Heterogeneity of study sample**

In contrast to previous studies that have investigated early UL behaviours in infants with perinatal or neonatal stroke (e.g.\textsuperscript{176-178}), this doctoral program investigated early UL behaviours in a sample of infants with unilateral and asymmetric bilateral brain lesions (i.e. arterial stroke, IVH, PVL). In addition, the asymBI sample comprised Caucasian infants recruited from multiple sites in Queensland, Australia and Pisa, Modena and Genoa in Italy. The heterogeneity of the asymBI sample allowed for variability in developmental trajectories of early reach to grasp development, which supports greater generalisability of findings for this very young and at-risk population.

**Assessment within the home environment**

All assessment occasions on the GRAB and the majority of six and 12 month follow-up assessments on the BSID III were performed in the home environment of each infant. This is another strength of this research, as infants were assessed in a familiar and naturalistic environment. Assessment of infants in their home provided infants with opportunities to demonstrate their abilities in the comfort and familiarity of their home environment; and minimised travel time for the families as they were visited at home by occupational therapists from the research team.

**7.4.2. Limitations**

There were a number of potential limitations identified in this research, which will be outlined below.

**Sample size**

The asymBI samples used in the validity study (n=24 for construct validity testing and n=6 for internal consistency testing), reproducibility study (n=6) and longitudinal study (n=26 at six month follow-up assessment and n=18 at 12 month
follow-up assessment) on the GRAB were smaller than the study sample proposed in the original protocol (n=32). This proposed sample of infants with asymBI, however, was based on examining the effects of a novel infant-friendly intervention, AOT. There was no available evidence to provide guidance on an adequate sample size for testing construct validity and predictive validity of the GRAB. Due to significant delays in recruitment of infants with asymBI across all sites, the recruitment period was extended until November 2014. Not all data was available at thesis submission, as four infants were not yet six months C.A. and eight infants were not yet 12 months C.A.

According to the COSMIN guidelines, the sample sizes for testing internal consistency and reproducibility of the GRAB were ‘poor’ (< 30). Each of these studies, however, involved significant amounts of data. Internal consistency was tested in a total of 180 toy presentations in six infants with asymBI and nine healthy infants. Reproducibility was tested in a total of 180 toy presentations in six infants with asymBI and seven healthy infants. For testing internal consistency and reproducibility of the GRAB, all toy presentations were analysed in clusters of six (to represent six toy presentations for each infant). The design effect (Deff) was calculated for testing internal consistency and reproducibility, which is the amount that a sample size needs to be multiplied in a study that involves cluster sampling. An equivalent sample size that reflected the amount of data that was contributed by each infant was then calculated, based on the total number of toy presentations and the Deff. The equivalent sample size for testing internal consistency of the GRAB in 180 toy presentations in 15 infants ranged from 51 to 75 infants. The equivalent sample size for testing reproducibility of the GRAB in 180 toy presentations in 13 infants ranged from 52 to 68 infants. According to the COSMIN guidelines, both equivalent sample sizes were ‘good’ (50-99); and were therefore adequate for detecting differences between and within groups in early reach and grasp behaviours at 14, 16 and 18 weeks C.A. on the GRAB. Furthermore, based on the available sample in the longitudinal paper at thesis submission (n=26/32 infants with asymBI and n=18/20 healthy infants at the six month follow-up assessment; and n=18/32 infants with asymBI and n=19/20 healthy infants at the 12 month follow-up assessment), there were differences detected between groups in motor development at six and 12 months on the BSID III.
It is acknowledged that the large number of toy presentations analysed in these studies were presented to a relatively small sample of infants. Therefore there was a potential for bias due to the reduced amount of variability that is to be expected in a small sample size.

*Paucity of reach and grasp at 18 weeks C.A.*

The GRAB demonstrated evidence of moderate to strong construct validity\(^{188}\) for identifying asymmetries in the development of early reach to grasp in infants with asymBI; as it identified a paucity rather asymmetry of early reach and grasp behaviours in infants with asymBI compared to healthy infants at 18 weeks C.A. This assessment occasion was selected to evaluate construct validity of the GRAB based on literature that has reported maturation of reach behaviours and emergence of grasp behaviours in healthy infants at this age (e.g.\(^{24,30,32,182,183}\)). It was therefore predicted that both groups would demonstrate the most mature reach behaviours and emerging grasp behaviours at the final assessment occasion of the GRAB; and infants with asymBI would demonstrate asymmetries between the potentially impaired and unimpaired ULs in unimanual reach and grasp behaviours compared to healthy infants. The alternative finding of the validity study may have reflected that reach and grasp behaviours were only emerging in infants with asymBI at 18 weeks C.A. As infants with asymBI demonstrated a paucity of behaviours at 18 weeks C.A., the GRAB was unable to detect asymmetries at this assessment occasion; which may reflect a limitation of the measure. Evaluation of reach and grasp behaviours beyond 18 weeks C.A. could be performed in future research, to investigate reach to grasp trajectories over 12 months.

*Scoring of video-clips*

The iterative process of developing the scoring method and criteria of the GRAB identified that the time required to score individual infants was significant compared to the 5.5-minute administration time of the structured play session. This finding suggests the utility of the GRAB as a measure for a research rather than clinical context.\(^{188}\) Furthermore, the scoring of some video-clips may have been impacted by reduced quality of video-recordings due to environmental factors (e.g. faulty video cameras, lighting, space restrictions) and set-up of the GRAB (e.g. camera angle and tripod height, occlusion of hands at the midline by the toys).
Missing data

There were some missing data for analyses of construct validity – six infants (14%) had incomplete video-recordings due to a faulty camera, or becoming fatigued and/or irritable during the assessment (validity paper, Chapter 4). There were also some missing data for analyses of predictive validity – four infants (8%) dropped out of the study prior to the six month follow-up assessment; and four infants (8%) were not yet six months C.A. at thesis submission. Prior to the 12 month follow-up assessment, seven (14%) infants dropped out of the study; and eight infants (16%) were not yet 12 months C.A. at thesis submission (Chapter 6). Infants dropped out of the study due to health issues or family circumstances. All infants with data at any assessment occasion were included in the analyses; and all available data from the GRAB were scored (i.e. 248/264 total possible toy presentations for construct validity; and 718/738 total possible toy presentations for predictive validity).

Follow-up assessment of infants with asymBI at 12 months C.A.

The mini-AHA rather than the BSID III Motor Scale would have been a more appropriate follow-up measure to assess infants with asymBI at 12 months C.A. At the commencement of the doctoral program (2011), however, the mini-AHA was not yet available (published in April 2013). The BSID III, however, is widely used both in research and clinical settings and enabled comparison of motor development at six and 12 months between the asymBI and healthy groups.

7.5. Considerations for future research and clinical practice

7.5.1. Recommendations for future research

The findings of this doctoral program provide an important contribution to the area of early detection and/or prediction of UCP in infants. Some specific recommendations for future research in early detection of UCP are provided below:

- In relation to RCTs of infants with or at risk of UCP, an individual patient data analysis could be utilised to analyse sub-groups and help to shed light on infant and intervention factors that may result in clinically meaningful outcomes. At present there is insufficient data to perform an individual patient data analysis in this young and at-risk population. Future RCTs of infants with or at risk of UCP could provide the data required for an individual patient data analysis.
Future research should involve infants with asymBI and evaluate asymmetries between ULs in early UL motor behaviours to detect and/or predict UCP; and carefully document new measures for this at-risk population.

The GRAB could be utilised in infants with asymBI beyond 18 weeks C.A. to map trajectories of reach to grasp; and to evaluate its potential to support other measures to detect UCP earlier (i.e. GMs assessment and the HAI).

An evaluation of concurrent validity of the GRAB with the HAI and the mini-AHA could be undertaken to investigate the relationship between the GRAB and these other measures of UL function in infants with or at risk of UCP.

Further validation of the GRAB could be performed with UL accelerometry by adding sensors on the toys, hands and arms of infants; to measure asymmetry of reach and grasp behaviours more objectively.

Development of other valid and reliable measures with adequate sensitivity to detect meaningful changes in response to early intervention; to improve UL reach and grasp and eventual bimanual manipulation for infants at risk of UCP.

7.5.2. Implications for clinical practice

The findings of this doctoral program provide an important contribution to the area of early detection and/or prediction of UCP in infants with asymBI. The implications for clinical practice for infants with asymBI based on this research are provided below:

- Early interventions that show promise for infants with asymBI include bilateral stimulation of hand function, AOT, environmental enrichment, eco-CIMT, mCIMT, hybrid CIMT, and a goal-directed training approach with an OT home program that is supplemented with intramuscular UL BoNT-A injections. The efficacy and feasibility of these interventions for this at-risk and very young population, however, remain unclear and require more rigorous research.

- Interventions such as mCIMT, hybrid CIMT, and OT supplemented with intramuscular UL BoNT-A injections may benefit infants with asymBI when they apply and/or integrate motor learning theory with ecological theory, involve goal-directed training and are delivered in infant-friendly environments, including the home.
Early interventions aiming to improve unimanual and bimanual UL motor outcomes for infants with asymBI require: (i) careful evaluation of efficacy; (ii) consideration of potential effects based on the theoretical underpinnings of the intervention, dosage, environment and method of delivery; and (iii) reporting of compliance, retention and adverse events.

Asymmetry of fidgety GMs at 12 weeks C.A. can be used as a definitive clinical sign of hemiplegia; while a paucity and/or asymmetries in unimanual reach to grasp and/or a paucity in bimanual reach to grasp at 18 weeks C.A. on the GRAB can indicate a strong clinical sign of emerging hemiplegia.

A combination of a GMs assessment, the GRAB and the HAI may help to identify at-risk infants who can benefit from early UL motor interventions during the first year of life.

The GRAB could be utilised in infants with asymBI beyond 18 weeks C.A. to evaluate UL motor outcomes in response to early UL motor interventions.

7.6. Conclusions

This doctoral program identified that there is limited evidence supporting the efficacy of UL motor interventions for infants with asymmetric brain injury, and that there is limited use of valid and reliable measures for: (i) early detection and/or prediction of UCP; (ii) examining the efficacy of early interventions; and (iii) quantifying meaningful change in response to intervention in this very young and at-risk population.

This doctoral program provides an important contribution to this limited evidence base, firstly by highlighting the potential of UL motor interventions such as mCIMT, hybrid CIMT, and OT supplemented with intramuscular BoNT-A injections to improve UL motor function in infants with asymBI. An effective CIMT program may benefit infants with asymmetric brain injury when it incorporates motor learning theory and/or ecological theory with goal-directed training, and is delivered in various practice environments (including the home). A goal-directed training approach with an OT home program, supplemented with intramuscular UL injections of BoNT-A may benefit infants and young children aged two to three years (as BoNT-A is not licensed for use in infants younger than two years). Secondly, this doctoral program introduces a new research measure, called the Grasp and Reach Assessment of Brisbane (GRAB), and provides the first evidence of its construct validity, internal
consistency, intra- and inter-rater reliability and agreement, and predictive validity. The GRAB demonstrated evidence of: (i) moderate to strong construct validity; (ii) strong internal consistency; (iii) strong intra- and inter-rater reliability; and (iv) strong intra- and inter-rater agreement as a quantitative research measure for detecting and evaluating the development of early unimanual and bimanual reach and grasp behaviours, both in infants with asymBI and healthy infants aged 14, 16 and 18 weeks C.A. Behavioural events (i.e. the number of unimanual contacts, grasps and bimanual grasps) are more reliable and more consistently measured on the GRAB compared to behavioural duration (e.g. the duration of unimanual contacts, and the duration of other behaviours).

Key findings of this research suggest that infants with asymBI may be less likely to demonstrate unimanual contacts, unimanual grasps and bimanual grasps; and score lower on the BSID III Motor Scale, compared to healthy infants. The GRAB can detect asymmetries in unimanual contacts and grasps at 14, 16 and 18 weeks C.A. in infants with clinical signs of hemiplegia at six months C.A. Preliminary findings suggest that behavioural events (i.e. the number of unimanual contacts, grasps and bimanual grasps) at 18 weeks C.A. on the GRAB are strong predictors of FM development on the BSID III Motor Scale in infants with asymBI at six months C.A.

Furthermore, this research suggests that the GRAB has potential to complement existing measures to detect UCP in infants with asymBI as it can be performed: (i) two weeks after a General Movements assessment at three months C.A.; (ii) at the same time as a Hand Assessment of Infants assessment at three months C.A.; and (iii) five months prior to a mini-Assisting Hand Assessment. The combination of these measures is promising for earlier detection of UCP in infants with asymBI; and together they have the potential to identify infants who may benefit from referral to early interventions such as mCIMT and AOT.
8. References

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9. Appendices


9.3. Stages of development of the scoring criteria and methods of the Grasp and Reach Assessment of Brisbane

9.4. Ethics approval – Queensland Children's Health Services Human Research Ethics Committee

9.5. Ethics approval – The University of Queensland Behavioural & Social Sciences Ethical Review Committee

9.6. Ethics approval – The Royal Brisbane and Women's Hospital

9.7. Ethics approval – Mater Health Services Human Research Ethics Committee

9.8. Ethics approval – Mater Health Services Human Research Governance

9.9. Ethics approval – Gold Coast Hospital and Health Service

9.10. Ethics approval – Stella Maris Foundation (Italy)

9.11. Study documents – Study flyers

9.12. Study documents – Study referral forms

9.13. Study documents – Study parent general information form


9.15. Study documents – Study video consent form

9.16. Study documents – Parent contact and general information form

9.17. Study documents – Study schedule form

9.18. Study documents – Action Observation Training sheet for parents


9.20. Study documents – Parent Diary template

9.21. Study documents – Medical History Checklist at study enrolment

9.22. Study documents – Medical History Update Checklist at 6 months

9.23. Study documents – Medical History Update Checklist at 12 months

9.24. Study documents – Study Checklist for each participant's chart
9.1. Paper 1 – Very early upper limb interventions for infants with asymmetric brain lesions

This paper comprises a book chapter that was published in September 2013. The bibliographic details are:
Chapter 13: Very early upper limb interventions for infants with asymmetric brain lesions

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Introduction

The main focus of early intervention for infants with asymmetric brain lesions who may progress to classification of unilateral cerebral palsy (UCP) is very early and accurate detection of the brain lesion, followed by provision of an enriched environment and training to maximise upper limb function during critical periods of development. The challenge for clinicians and researchers are the limited quantitative tools available to identify the problem and measure progress as well as the paucity of evidence for efficacy of very early upper limb rehabilitation. In this book chapter we will: (1) focus on the current knowledge of critical periods of early upper limb development and the potential neural correlates; (2) summarise the evidence for efficacy of current interventions; and (3) explore new options for early stimulation of the damaged cortex to achieve better symmetry of upper limb motor development. Lessons learned from our clinical trials of intensive upper limb interventions in school-aged children with UCP, including the impact of dose, density and components of training on neuroplasticity, will be discussed in light of the implications for training the young infant with an asymmetric brain lesion in the first two years of life.

The problem

Infants with early asymmetric brain injury are at high risk of developing congenital hemiplegia as a result of presumed prenatal, perinatal or postnatal brain injury. The underlying injuries usually consist of periventricular white matter damage (e.g. periventricular leukomalacia or venous infarctions), cortical and/or deep grey matter damage, (e.g. arterial ischaemic stroke), and less frequently, brain malformations of one hemisphere (e.g. focal cortical dysplasia or unilateral schizencephaly). Congenital hemiplegia is the most common type of Cerebral Palsy (CP), with a prevalence of 1 in 1300 live births. These infants have impaired upper limb motor function and can experience difficulties participating in activities of daily life (e.g. feeding, play and self-care). There are, broadly speaking, two common clinical presentations of asymmetric brain lesions: early or delayed. Early presentation consists of perinatal onset of neurological symptoms, or seizures, or reduced movement at 24 to 48 hours post-birth with verification on cranial ultrasound and/or magnetic resonance imaging (MRI) of the presence of a unilateral or asymmetric brain lesion. Specific imaging protocols may be needed for the diagnosis in the early phases, such as diffusion MRI to identify an acute stroke in the first hours
or days. In a delayed presentation, the infant may have an initially uncomplicated perinatal course and may not show signs of stroke or asymmetric brain injury until three to seven months of age when unilateral weakness and early hand preference start to manifest.

_Definitive diagnosis of hemiplegia_

The current most predictive tools for early diagnosis of CP are a combination of brain MRI at term and a general movements (GMs) assessment in the fidgety period. Specifically, GMs at 1 month and 3 months post-term age are highly associated with white matter abnormalities on MRI at term age. The GMs assessment is a well-validated and reliable tool, and is more sensitive at predicting CP than other motor assessments used in infancy. Neuromotor assessments utilised in the neonatal period have strong validity to detect CP in infants born preterm on criterion assessments at 12 months corrected age (such as the Bayley Developmental Scales II and III); moderate evaluative validity (on the Test of Motor Impairment, TIMP), as well as prediction of minor motor difficulties using the GMs. The classification of early writhing general movements is abnormal although asymmetries are not yet visible, while asymmetry of fidgety GMs around 12 weeks post-term can be the first definitive clinical sign of hemiplegia. The asymmetry of GMs at fidgety period (12 weeks post term) has strong validity for early prediction of hemiplegia. Very early detection of hemiparesis frequently requires serial evaluation of subtle signs of interlimb differences or asymmetries in muscle resistance to passive movement, muscle stiffness, upper limb reaching (both spontaneous and purposeful), and grasp strength. Both bimanual and unimanual reaching with early strong hand preference at four to six months of age can be considered to be a strong sign of early hemiplegia. Studies of infants who have sustained an early perinatal stroke from 4 to 7 months corrected age have suggested that until reach to grasp behaviours have emerged, an asymmetry may not be clearly evident so that a hemiparesis may not be confirmed.

_Critical periods of typical upper limb motor development_

Upper limb skills of typically developing infants generally develop in several stages: (1) discovering the hand; (2) visually regarding the hand; (3) visually exploring objects in space; (4) swiping at objects; (5) contacting objects; (6)
ineffectively grasping objects; and (7) developing prehensile movements to better grasp objects. These stages of prehension are not consecutive and often overlap (Table 9.1.). Prior to the onset of reach, infants have been observed to demonstrate prehensile movements that provide multimodal input about their upper limb function within their environment and sensorimotor experiences that provide early motor programmes for upper limb control. Grasping involves the shaping and coordinated movements of fingers and rotation of the wrist in a manner that anticipates the size, shape and physical features of the target object.

All the components of prehension, including visual regard, reach, grasp, manipulation, pulling, pushing objects and release, can be impacted by an early brain lesion. In typically developing infants hand preference is strong initially and often varies (e.g. ). Handedness in infants can be observed when they undertake bimanual tasks. Switching hand preference while manipulating an object happens early in motor development, prior to 6 months of age. There is evidence that fine motor skills such as reaching, grasping and releasing develop at variable and often overlapping time points (see Table 9.1.1.).

At 5 months of age, typically developing infants demonstrate preparatory forearm rotation and hand pre-shaping based on a toy’s position, shape and size, which leads to successful grasping. Infants with early asymmetric brain damage and visual deficits can start to develop maladaptive prehensile skills such as asymmetric reaching, increased forearm pronation, ineffective hand opening and pre-shaping of the hand to the toy. These maladaptive prehensile skills result in inefficient manipulation (such as contacting and grasping toys) and difficulty releasing objects.

**Cortical reorganisation after an early brain lesion: a critical window**

There is some evidence to suggest that for infants with early brain lesions, important phases of sensorimotor reorganisation occur during their first year of life. After a brain lesion has occurred, development of the damaged cortex is compromised and its remaining contralateral corticospinal (CS) pathways (which connect the damaged cortex to the impaired upper limb) stop developing. Eventually, the synaptic space that these pathways initially occupied is taken over by the more active ipsilateral pathways (which connect the intact cortex to the impaired upper limb). Both sets of CS pathways compete for synaptic space, which results in the ipsilateral CS pathway outgrowing the contralateral CS pathway. As a
consequence, two main types of brain reorganisation can be observed after early asymmetric brain injuries. Ipsilesional reorganisation (i.e. reorganisation occurring within some spared cortical tissue of the damaged hemisphere) allows for the motor cortex of the damaged hemisphere to become reconnected to the spinal cord, and is usually what is seen in adults following stroke. Contralesional organisation (i.e. reorganisation occurring in the undamaged cortex) is based on existing ipsilateral motor projections remaining intact, instead of becoming retracted within the first months of life. This specific alternative type of reorganisation is possible if the lesion occurs early in development. It allows the undamaged cortex to directly control both upper limbs and often involves the dissociation of the primary sensory and motor pathways, resulting in limited upper limb functional activity. On these grounds, the first three to six months of life following an asymmetric brain lesion appear to be a critical window of opportunity for very early intervention. This intervention could be aimed at maintaining cortical motor control within the affected hemisphere by activating the damaged sensorimotor (SM) cortex, and thus enhancing its competitive ability to develop alongside the intact SM cortex, as well as ameliorating the effects of the lesion on upper limb motor activity. A crucial role in predicting the type of functional reorganization is certainly influenced by the degree of involvement of the CS tract. A perilesional reorganization can be unachievable in the case of a massive destruction of the corticospinal tract of one hemisphere. Nevertheless, when some sparing of the tract is present, some other factors are likely to come into play, and early intervention can have the potential to shape cortical reorganization and potentially ameliorate the eventual outcome (Figure 9.1.1.).

A recent review of studies in a feline model provides support for the initiation of prehensile training in infants before 6 months of age. The authors have highlighted the close correlation between the activity of the CS tracts and the strength of the synaptic connections with spinal motor circuits. This supports the hypothesis that early brain damage might initiate a vicious cycle in which damaged CS tracts are competitively disadvantaged for maintaining spinal synapses, resulting in secondary reductions in these connections. More recently, the same group has tested the ensuing hypothesis that targeted activation of the spared CS tracts should lead to functional improvement, by exploring the effects of early intervention in cats with primary motor cortex (M1) inactivation. Three experimental groups were
studied. In the first group, the limb ipsilateral to inactivation was restrained, forcing use of the contralateral, impaired limb, for the month following the inactivation (early restraint alone). In the second group, the early restraint was supplemented with daily training of a reaching task with the contralateral forelimb (early restraint + training). In the third group, both restraint and training were postponed to feline adolescence (late restraint + training). Outcome was measured at three levels by analysing: (1) CS tract spinal connections; (2) M1 motor maps; and (3) motor performance. Interestingly, restraint alone was able to restore CS tract connectivity but failed to affect M1 motor maps or motor function; while late training affected both CS tract connectivity yet failed to impact on M1 motor maps or motor function, while late training impacted on both CS tract connectivity and motor maps (however, it failed to induce significant functional recovery). The only intervention affecting all three measures of outcome was the one based on early restraint combined with training. Altogether these findings suggest that in order to achieve significant motor improvement, a complex network of integrated functions of the CS system needs to be re-established, which targets intervention at multiple hierarchical levels.

The importance of a multilevel network in the reorganization of the CS system has been suggested by recent work in humans with congenital hemiplegia. Evidence from advanced diffusion imaging has suggested that the developing connectivity and symmetry of the thalamocortical pathways connecting M1 with the motor thalamus is at least as important as the symmetry of the CS tracts for upper limb unimanual capacity and bimanual coordination in children with congenital hemiplegia. Our group studied 16 children with congenital hemiplegia, of whom 9 were classified as having periventricular leukomalacia and 7 were classified as having predominantly deep gray matter lesions, according to the Krägeloh–Mann qualitative scheme. Advanced diffusion imaging utilising the HARDI model (high angular diffusion imaging) was performed to elucidate the symmetry in the CS (motor) and the thalamocortical (sensorimotor) tracts (Figure 9.1.2., Table 9.1.2.). Surprisingly, the sensorimotor thalamic tracts were more significantly correlated with paretic hand functions than were the CS tracts. These data suggest that functional outcome is not only related to the integrity of the CS tract (the final output) but rather to the integrity of a wider neural integrated network. Our data also support the concept that the motor system requires feedback from sensory systems to shape the development of the motor cortex and efferent motor pathways. To date, upper limb rehabilitation
has focused primarily on interventions to promote activation of the motor tracts with little regard to the preservation and balance of input to the sensory tracts.

**Current evidence for early upper limb interventions for infants with hemiplegia**

Upper limb rehabilitation for school-aged children with hemiplegia focuses on improving unimanual and bimanual function and enhancing participation (ICF). A recent meta-analysis of all non-surgical interventions provided evidence for modest improvements in unimanual and bimanual co-ordination using various models of constraint-induced movement therapy (CIMT), bimanual intensive training, a combination of CIMT and bimanual training, and adjunctive use of intramuscular botulinum toxin A (BoNT-A) injections combined with upper limb training.

While early interventions for infants at risk of developing congenital hemiplegia are considered to be very important, the reality is that rehabilitation programs commonly do not commence until six months of age. This may be due to a delayed diagnosis, for those infants not showing early acute signs of brain damage, or to a lack of consensus on the safety and efficacy of early interventions, which prevents early intervention from being included in service programs. To date, no review has investigated the efficacy, feasibility, compliance and impact on motor development of upper limb interventions in improving upper limb motor activity specifically for infants and young children aged less than three years with early brain injury or CP. Under the age of three years, the evidence for applying upper limb interventions remains unclear.

A recent systematic review of non surgical interventions (including modified CIMT, bimanual training, physiotherapy and occupational therapy) has examined the efficacy for improvements in unimanual capacity of the hemiplegic limb, bimanual co-ordination and the amount and quality of hand use in randomised clinical trials for infants and toddlers up to 2.5 years of age with asymmetric brain lesions (Perez et al., unpublished data). In three systematic reviews and 17 randomised clinical trials only six per cent of the 1446 participants with UCP were aged less than 2.5 years.

In this systematic review nine randomised controlled trials (RCTs) used modified constraint-induced movement therapy (mCIMT, modified for a paediatric population) in samples including infants up to 2.5 years of age, with the total dose varying from 16 hours to 210 hours. Four studies of mCIMT found a small treatment effect on bimanual coordination for CIMT.
compared with control groups (OT, physiotherapy [PT], neurodevelopmental therapy [NDT]). Only one study found that mCIMT effects were sustained for the treatment group at 17 weeks follow-up in an ecologically delivered programme of constraint with activity-based practice.\(^5\) One study of CIMT found a clinically important change post-treatment for amount of use and quality of movement using constraint of the unimpaired limb with a cast and shaping to train the impaired limb.\(^{113}\)

Four RCTs used intramuscular botulinum toxin A (BoNT-A) injections for forearm muscles with spasticity interfering with function as an adjunct to goal-directed training.\(^{126,220-222}\) As yet, safety and efficacy of intramuscular BoNT-A is not determined for use in infants with congenital hemiplegia less than two years of age. The potential for adverse events (although short acting and reversible), as well as muscle weakness and atrophy in school-aged children,\(^{223,224}\) promotes caution for the use of neuromuscular blockage of the overactive muscles in young infants with asymmetric brain lesions under two years of age.

In our systematic review, none of the study populations solely comprised participants under 2.5 years of age (Perez et al., unpublished data). Seven of the 17 RCTs reported adverse events, some of which were thought to be associated with the intervention, including tolerating CIMT,\(^{116}\) physical symptoms that may have been associated with BoNT-A injections or the conscious sedation.\(^{222}\) As it was not possible to separate the number of adverse events related to participants under the age of 3 years, the feasibility and compliance of these interventions for this younger age group is unclear. The existing evidence suggests small effects of CIMT with activity-based practice and shaping to improve unimanual capacity and bimanual coordination (Perez et al., unpublished data).

**Potential early interventions for infants with asymmetric brain lesions**

There are several promising very early interventions for infants with asymmetric brain lesions that focus either on (i) bilateral stimulation of hand function (ii) constraint induced movement therapy ;and (iii) action observation training. To date, there are no published randomised trials to confirm the efficacy and feasibility of these interventions in infants.
(i) Early bilateral stimulation of reaching and grasping with motor and sensory components

Traditional approaches to early upper limb training have focused on bimanual delivery of sensory stimulation (stroking, tactile stimulation) and either equal presentation of toys to both upper limbs or increased presentation to the impaired side. Few studies have ensured equal stimulation of both limbs in a controlled manner and have tended to focus on over stimulation with visual, tactile stimulation and object presentation on the impaired side. While bimanual grasp develops in the typically developing infant from 3 months post-term, bimanual co-ordination of objects may not mature until 18 months post-term. This provides a challenge for delivery of bimanual training as developed in older children with congenital hemiplegia, where the nature of the task and objects require bimanual use with varying amounts of use of the impaired hand as an assisting hand. In the young infant, equal presentation of toys to both upper limbs and the bilateral facilitation of reaching and grasping are considered to be an important component to develop early motor representations in the brain. The unimpaired hand is thought to act as a template for the development of reaching in the impaired hand. The challenge is to deliver equal training for the infant with an asymmetric brain lesion where overcompensation with the unimpaired hand and increased lateralisation of the motor cortex can lead to maladaptive plasticity. The challenge remains as to how to stimulate the damaged sensory motor cortex before volitional movement develops (before 3 months) to ensure equal input to both the motor and sensory pathways.

(ii) Infant modified constraint induced movement therapy

Considerable experience and evidence has been determined for various models of a child-friendly form of CIMT for school-aged and preschool-aged children (down to 18 months corrected age). Various constraints have been utilised for the unimpaired hand, ranging from a glove with rigid insert; a sling; gentle manual restraint; and rigid plaster casts. A comprehensive meta-analysis has not demonstrated superior effects for 24 hour use of the rigid cast over 21 days compared to shorter doses of constraint of the unimpaired hand with a glove (six hours per day for 10 days). In children under 18 months with an asymmetric brain lesion, we propose the use of a more child-friendly mitt that enables some gross assistance with the gloved hand in bimanual tasks and limits manipulation of the
unimpaired hand, while still enabling some training of bimanual tasks (Figure 9.1.3A.).

Vigorous debate has ensued regarding the type constraint and the dose of constraint required; however, the type and intensity of accompanying training of the impaired limb appears to be more critical to success. Activity-based practice in the context of ecologically friendly environments such as the preschool and home or in intensive day camps and with motivating themes appear to be key ingredients to successful training of unimanual capacity and compliance with the constraint. Our own study, the “INCITE” trial, employed a novel circus theme during the activity-based day camps to ensure practice with the ‘just right challenge’ and minimal frustration with the constraint (glove; Figure 9.1.3B.), achieving high study retention.

A major consideration for current approaches of CIMT and bimanual therapy (BIM) for children with UCP is that dosage of intervention vary between 60 to 120 hours of training. Recently we have concluded two single blind (investigator masked) matched pairs (children were matched for age, gender, side of hemiplegia and unimanual capacity) then randomized in a comparison trial directly comparing mCIMT (with a glove and intensive activity-based practice) with an equal dose of bimanual training (BIM) where the activities all demanded equivalent use of both hands. These trials directly comparing equal dosages of a block of CIMT or BIM in the same environment provide evidence for the differential effects on unimanual capacity and bimanual performance; there are similar effects on translation to enhanced participation in goal areas and improvements in quality of life, features of best responders, and the long term retention of these effects at 12 months after delivery.

In a related study, our team has also addressed the question as to whether sufficient effect might be achieved at lower dosages (total dose of 30 hours compared to 60 hours). In comparing the efficacy of two intensities of CIMT and BIM on unimanual capacity and individualized goals, we hypothesized that half the dose of training would still have 75% effect and would therefore be more feasible. These studies of school-aged children with CP provide important information that ‘half the dose may not be enough, and double to dose may be too much’. The question of the size of the therapy pill in young infants with asymmetric brain lesions is a critical one.
In infants under 2 years of age, modifications have been proposed to reduce the period of constraint down to a few hours per day, to vary the type of constraint including gentle manual guidance or a padded glove; to ensure the type of accompanying training is activity based; or shaping. Recent studies, in a feline model, however, suggest caution in constraining the unimpaired limb and the impact in development of the CS projections. Early use of CIMT may lead to increased lateralisation of the CS projections with greater chance of contralesional reorganisation (see Figure 13.1). The limitations of CIMT in the young infant include reduced sensory feedback from the unimpaired hand, reduced active use of the unimpaired hand with limitation for its use as a template for developing motor control in the impaired hand, as well as limitations in the development of bimanual grasp. An alternative may be the use of either gentle manual constraint of the unimpaired hand during motor training (toy presentation combined with sensory stimulation) or the use of short periods of a material mitten on the unimpaired hand to reduce the manipulative abilities of the unimpaired hand (see Figure 9.3.), thereby enabling a more infant-friendly form of constraint. To date, none of these methods have been tested in adequately powered clinical trials with infants. A further consideration is the provision of evidence to determine the impact of early modified constraint on the development of both CS projections and spinothalamic projections.

(iii) Early action observation training

Action Observation Therapy is a recent approach that has been shown to effectively improve upper limb motor function in adults with chronic stroke and is being investigated in school-aged children with UCP. Intervention is based on action observation, whereby new motor skills can be learned by observing motor actions. AOT is a rehabilitative methodology that combines the observation of daily actions with physical training of the observed actions, to reinforce the activation of motor areas. An example of this is watching video sequences of goal-directed upper limb actions in daily life activities, followed by repetitive practice of the observed actions with the impaired upper limb (see for an example in school-aged children with congenital hemiplegia). This process appears to be facilitated by the Mirror Neuron System (MNS). It has been proposed that the MNS codes for the execution of motor actions, which implies that: (i) there are pre-existing motor representations in the motor cortex of hand movements; and (ii) the ability to match
the physical features of an object with appropriate hand movements in order to grasp the object effectively is innate.52,77,82

Recent evidence suggests that this mechanism is present from birth, and yet little is known about its role in motor development.241 Use of Action Observation Training (AOT) in school-aged children with congenital hemiplegia76 and adults following stroke75 provides promising results for the recovery of unimanual capacity accompanied by brain reorganisation. Our group has commenced an infant modified version called upper limb baby early action observation training (UP-BEAT, Australian Research Council grant DP110104292). The feasibility, efficacy and neural correlates of AOT are being compared in a sham control randomised clinical trial (Figure 9.1.4.).

In animal and human adult studies, AOT has been shown to be an effective method to increase cortical excitability of the sensorimotor cortex. Based on the hypothesis that the same activation can be induced in young infants, we predict that a training based on movement observation (very early observation of grasping, Figure 9.1.4A.), coupled with actual hand motor activity (contacting the toy, and later grasping and reaching), will enhance the excitability of the sensorimotor cortex, will accelerate the maturation of the CS tracts as well as the shaping of spinal motor circuits. This will potentially result in the modification of various quantitative and qualitative measures of grasping and reaching behaviours (e.g. the age at onset of reaching, frequency, symmetry, movement properties, grip power), both in healthy infants and in those with congenital brain damage.

A sham control study design is being used for the RCT, in consideration that it would be unethical to give no intervention to an at-risk population. The sham control will consist of a standard intervention that does not include the active component of the intervention for the treatment group (toy presentation with no observation of grasping, Figure 9.1.4B and 9.1.4C.). Infants with an asymmetric brain lesion (e.g. arterial stroke, venous infarction, intraventricular haemorrhage or periventricular leukomalacia) that have been identified through a neonatal ultrasound or neonatal MRI are entered into the study. Parents of the active training or AOT group will repeatedly show the infant a grasping action on a set of toys, presented in random order (Figure 9.1.4A). Parents of the standard care or toy observation training (TOT) group will show the infant the same set of toys, also presented in random order, without demonstrating the grasping action (Figure 9.1.4B and 9.1.4C.). This study
will determine if AOT can influence the early development of reaching and grasping of typically developing infants and improve the upper limb motor activity of infants with asymmetric brain lesions. Very early intervention should also be combined with current upper limb training methods (e.g. unimanual and bimanual activity-based training) as soon as infants can reach voluntarily, to reinforce the growth and connectivity of cortical pathways and consolidate learning of upper limb motor skills. Based on the hypothesis that the same activation can be elicited in infants, it is predicted that AOT will enhance the excitability of the SM cortex, accelerate the maturation of the CS tract and the shaping of spinal motor circuits. While AOT training in infants is still undergoing experimental confirmation it is hoped that it will offer an opportunity to stimulate the damaged motor cortex during that first critical period (birth to 4 months) to minimize asymmetries in development of the CS tracts.

(iv) Adjunctive therapies

For infants with asymmetric brain lesions, there is currently no evidence for safety or efficacy for the use of adjunctive interventions such as intra-muscular injections of BoNT-A, splints for assistance, casting to stretch muscles with contracture and/or the use of neoprene thumb splints or taping to assist or provide feedback for overactive movements (i.e. thumb in palm) as utilised in school-aged children with hemiplegia. There is developing evidence that pharmacological interventions may have very negative effects on the developing neuromuscular system, so that use of BoNT-A in the very young infant should be viewed with extreme caution.\textsuperscript{223,224} Adjunctive interventions which immobilise the hand and arm, reduce sensory feedback, limit activity-based practice, bimanual coordination and restrict the development of motor maps should also be viewed with caution.

(v) Translation into the real world

To date, few clinical trials of mCIMT and BIM in school-aged children with UCP have measured outcomes until 12 months follow-up with positive benefits for the continued improvement in upper limb activity.\textsuperscript{240} Our large single blind randomised trial directly comparing mCIMT with activity-based practice to an equal dose of intensive bimanual training (where all tasks required bimanual coordination) led to differential improvement in activity limitations.\textsuperscript{240} Children in each arm of the RCT ‘gained what they trained’ in that while both programmes were effective, CIMT had a differential effect on unimanual capacity and BIM improved bimanual coordination.\textsuperscript{240} These improvements translated to reductions in participation
restrictions only in goal areas selected by the child that were context-specific.\textsuperscript{237} There are some promising effects of improvements in domains of quality of life, with both models of intensive upper limb training providing evidence that an intensive activity-based training can have more global benefits.\textsuperscript{238} Our INCITE trial also provided the first evidence for the differential effect of CIMT compared to BIM to improve neuroplasticity, confirmed on both transcranial magnetic stimulation (TMS) and functional MRI (fMRI).\textsuperscript{242} These series of studies confirm that mCIMT is best at ‘turning on the motor cortex and improving unimanual capacity’; however, it should be followed by BIM to consolidate these effects into improvements in bimanual coordination which encompass at least 75\% of daily hand use.

The next challenge is to provide upper limb training programmes that are able to be translated into the home for continued incremental practice at high intensities. Optimal brain plasticity occurs when interventions incorporate the following key elements: (1) intensive task oriented repetition; (2) incremental challenges with increasing difficulty; and (3) the presence of motivators or rewards.\textsuperscript{243,244} Web-based multimodal training programmes such as ‘Mitii\textsuperscript{®}: Move it to improve it’ provide promising data for improvements in manual ability combined with physical and cognitive challenge for school-aged children with UCP,\textsuperscript{245} see Chapter 15. Programmes such as Mitii, which provide a multimodal approach with multi-system incremental challenges at high intensity, are more likely to drive neuroplasticity and have lasting benefits. Web-based training can provide expertise from central based virtual trainers to enable progressive incremental challenge of daily training in the home. New environmental training mats and toys with sensors for measurement and provision of visual, auditory and tactile stimulation are currently being developed, which if linked via cable to an internet-link camera will enable training and monitoring in the home with external expert advice. These web-delivered or monitored training environments offer new opportunities for prehensile training of young infants at home at high intensities, with incremental challenge and frequent expert feedback. The efficacy of these approaches are currently being tested in randomised trials.
Future Directions

Very early training of prehensile skills for young infants with signs of hemiplegia is likely to be beneficial as it can take advantage of neural plasticity associated with skill development before learned non-use, musculoskeletal impairments or ineffective behaviours can develop. An important consideration in testing the efficacy of new interventions to improve manipulative skills is the role of neural recovery alone, or whether recovery is augmented by the specific training provided. Randomised clinical trials with a sham control are therefore essential. There are some lessons learned from our studies of school-aged children with UCP regarding the type (model), intensity, use of incremental challenges, motivation and the task relatedness of training which need to be explored to determine the components of success in infants with asymmetric brain lesions.

The small numbers of infants detected very early highlights the need for comprehensive multi-site trials to examine the efficacy of new prehensile training models for young infants with asymmetric brain lesions. An important consideration is the measurement of neural correlates to determine the positive or negative plasticity accompanying changes in prehensile development.
Table 9.1.1. Presumed timing of development of reaching, grasping and releasing in infants.

<table>
<thead>
<tr>
<th>General Motor Skill</th>
<th>Specific Fine Motor Skill</th>
<th>Proposed Time Point (post-term months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reaching</td>
<td>Visually attending to objects carefully while reaching ineffectively</td>
<td>1 – 3 months</td>
</tr>
<tr>
<td></td>
<td>Demonstrating finger, eye and hand adjustments to better contact objects</td>
<td>4 months</td>
</tr>
<tr>
<td></td>
<td>Reaching objects in a controlled manner</td>
<td>6 months</td>
</tr>
<tr>
<td>Grasping</td>
<td>Reflexively grasping objects</td>
<td>Birth until 4 months</td>
</tr>
<tr>
<td></td>
<td>Beginning to use a voluntary palmar grasp with both hands</td>
<td>3 months</td>
</tr>
<tr>
<td></td>
<td>Beginning to grasp with the preferred hand</td>
<td>5 months</td>
</tr>
<tr>
<td></td>
<td>Using a pincer grasp</td>
<td>9 months</td>
</tr>
<tr>
<td></td>
<td>Using a controlled grasp</td>
<td>14 months</td>
</tr>
<tr>
<td>Releasing</td>
<td>Having a basic ability to release objects from grasp</td>
<td>12 – 14 months</td>
</tr>
<tr>
<td></td>
<td>Demonstrating controlled release of objects</td>
<td>18 months</td>
</tr>
</tbody>
</table>

Bimanual coordination

<table>
<thead>
<tr>
<th>Specific Fine Motor Skill</th>
<th>Proposed Time Point (post-term months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Releasing</td>
<td>birth until 4 months</td>
</tr>
<tr>
<td>Bimanual coordination</td>
<td>birth until 4 months</td>
</tr>
</tbody>
</table>


Table 9.1.2. Corticothalamic tracts (CTT) pathways were more highly correlated with baseline hand function than corticospinal tracts (CST).

<table>
<thead>
<tr>
<th>AI [(C-I)/(C+I)]</th>
<th>Jebsen</th>
<th>Muul</th>
<th>AHA</th>
</tr>
</thead>
<tbody>
<tr>
<td>CST</td>
<td>0.39</td>
<td>-0.23</td>
<td>-0.35</td>
</tr>
<tr>
<td>CTT</td>
<td>0.80*</td>
<td>-0.67*</td>
<td>-0.62*</td>
</tr>
</tbody>
</table>

Key: CTT= Corticothalamic tracts; CST= Cortico-spinal tracts.
AI= Asymmetry Index; Jebsen= Jebsen Taylor hand Function test, MUUL= Melbourne Unilateral upper limb assessment; AHA= Assisting hand Assessment.
Figure 9.1.1. Diagrammatic representation of ipsilesional versus contralesional reorganisation following an asymmetric brain lesion and impact on upper limb function. The extent of primary motor cortex (M1) damage can be the strongest predictor of the type of reorganisation in case of very mild (left column) or very severe (right column) injuries. When M1 damage is of intermediate size (central column) type of motor reorganisation can be harder to predict and is likely to be significantly influenced by intervention.


Figure 9.1.2. Top left is motor cortex (pre + postcentral) to brainstem through the Posterior Limb of the Internal Capsule (PLIC), top right is motor cortex (pre + postcentral) to brainstem through the thalamus. Bottom row shows cross-sectional area of the same tracts as above at the level of PLIC/thalamus.

Figure 9.1.3. Two examples of modified Constraint Induced Movement therapy suitable for young children with congenital hemiplegia using (A) soft material mitten on the unimpaired hand to constraint the manipulative abilities of the dominant and to shift the role of manipulation to the hemiplegic hand or (B) a glove with rigid insert accompanied by group activity-based practice.

Figure 9.1.4: Examples of (A) Action Observation training (AOT) and (B) Toy Observation Training (TOT) in the UPper limb Baby Early action-observation Training study (UP-BEAT).

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Study Protocol

Title
UP-BEAT (Upper Limb Baby Early Action-observation Training): Protocol of two parallel randomised controlled trials of action observation training for typically developing infants and infants with asymmetric brain lesions

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Competing Interests
The authors declare they have no competing interests.

Authors’ Contributions
RB is the Australian Research Council (ARC) chief investigator A and AG is the partner investigator on the study. RB, AG and JZ were responsible for writing and obtaining the major study grant from the ARC. AG defined the original study protocol, and together with RB, KP, LF and IF led the modification of the study protocol to the present study design and format. They also designed the therapy contents. RB, AG, JZ, KP and MP are responsible for all ethics applications and the ethical reporting of the study. RB, KP, LF, IF, and MP are responsible for recruitment, data collection and implementation of the study in Queensland. AG, VB, FC and GT are responsible for recruitment, data collection and implementation of the partner investigation in Italy. AG is responsible for the design, implementation and data collection in Italy and analysis of the EEG component of the study for infants with asymmetric brain lesions. KP will be involved with the EEG data collection in Queensland. SR and VM will assist AG in the EEG. VS is responsible for the design, implementation and analysis of the Imitation Assessment component of the study. KW will be involved with the BSID III assessments for infants with asymmetric brain lesions. RB, JZ and AG will co-supervise the PhD student (MP). RB, AG, JZ and MP will take lead roles on preparation of publications on the clinical outcomes of the study and RB and AG will take lead roles on the neuroscience publications from the study. All authors have read and approved the final manuscript.

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Structured Abstract

Introduction

Infants with asymmetric brain lesions are at high risk of developing congenital hemiplegia. Action Observation Therapy (AOT) has been shown to effectively improve upper limb motor function in adults with chronic stroke. AOT is based on action observation, whereby new motor skills can be learned by observing motor actions. This process is facilitated by the Mirror Neuron System, which matches observed and performed motor actions. This study aims to determine the efficacy of AOT in: (1) influencing the early development of reaching and grasping of typically developing infants and (2) improving the upper limb activity of infants with asymmetric brain lesions.

Methods and Analysis

This study design comprises two parallel randomised sham controlled trials (RCTs) in: (i) typically developing infants (cohort I); and (ii) infants with asymmetric brain lesions (e.g. arterial stroke, venous infarction, intraventricular haemorrhage or periventricular leukomalacia; cohort II). Cohort II will be identified through a neonatal ultrasound or neonatal Magnetic Resonance Imaging. A sham control will be used for both RCTs, in consideration that it would be unethical to give no intervention to an at-risk population. Based on a 2-tailed t-test of 2 independent means, significance (alpha) level of 0.05, 80% power, predicted effect size of 0.8 and a 90% retention rate, we require 20 participants in each group (total sample of 40) for cohort I. Sample size for cohort II was based on the assumption that the effect size of the proposed training will be similar to that found by Heathcock et al. (2008) in preterm born infants (n=26) with a mean effect size of 2.4. Given the high effect size, the calculation returned a sample of only 4 participants per group, on a 2-tailed t-test, significance (alpha) level of 0.05 and 80% power. As cohort II will consist of two subgroups of lesion type (i.e. arterial stroke and venous infarction); we have quadrupled the sample to include 16 participants in each group (total sample of 32). Infants will be randomised to receive either Action Observation (AOT) or standard Toy Observation Training (TOT). Both interventions will be of four weeks’ duration, from the infant’s 9th to 13th post-term week of age. Three sessions of five minutes will be performed each day for six days per week (total of six hours over 28 days). Parents of the AOT group will repeatedly show the infant a grasping action on a set of three toys, presented in random order. Parents of the TOT group will show the infant the
same set of three toys, in random order, without demonstrating the grasping action. At 14, 16 and 18 weeks, quantity and quality of reaching and grasping will be measured using the Grasping and Reaching Assessment of Brisbane; symmetry of reaching and grasping will be measured using the Hand Assessment of Infants (HAI); and pressure of grasping for each hand with a customised pressure sensor. At six months CA the primary outcome measures will be the HAI and the Bayley Scales of Infant and Toddler Development (third edition; BSID III), to measure cognitive and motor development. At eight months the HAI will be used as well as electroencephalogram, to measure brain activity and cortical coherence. At 12 months, the primary outcome measures will again be the HAI and the BSID III.

Ethics

Ethical permission to conduct the study has been obtained from the relevant Human Research Ethics Committees at the Royal Children’s Hospital, Brisbane (HREC/09/QRCH/134), The University of Queensland (2009001870), The Royal Brisbane & Women’s Hospital (HREC/09/QRCH/134), The Mater Children’s Hospital and The Mater Mother’s Hospital (1814MC), the Stella Maris Scientific Institute and University of Pisa in Italy (43/2011).

Dissemination

This paper outlines the theoretical basis, study hypotheses and outcome measures for two parallel RCTs comparing the novel intervention Action Observation Training with standard Toy Observation Training in: (1) influencing the early development of reaching and grasping of typically developing infants, and (2) improving the upper limb motor activity of infants with asymmetric brain lesions.

Trial Registration

ACTRN1261100991910

Web address of trial

**Background**

Infants with asymmetric brain lesions (e.g. intraventricular haemorrhages, periventricular leukomalacia, arterial strokes and venous infarctions occurring on one side or more involved on one side of the brain) are at high risk of developing congenital hemiplegia by the end of their first year of life. The incidence of asymmetric brain lesions at birth is 1-2 of every 1000 newborns. 61 Congenital hemiplegia is the most common type of Cerebral Palsy (CP), with a prevalence of 1 in 1300 live births. 61 The economic impact of CP is substantial. In 2007, the financial cost of CP was estimated at Aus$1.47 billion, with $124.1 million of that cost directly attributed to intervention costs. 246 Approximately 43% of these costs are covered by the families of individuals with CP, with the remaining 57% by various levels of government. 246

The main focus of early intervention for infants with asymmetric brain lesions who may progress to classification of UCP is very early and accurate detection of the brain lesion, followed by provision of an enriched environment and training to maximise upper limb function during critical periods of development. The challenge for clinicians and researchers is the limited number of tools available to identify the problem and measure progress, as well as a paucity of evidence for efficacy of very early upper limb rehabilitation.

There are, broadly speaking, two common clinical presentations of asymmetric brain lesions, early or delayed. Early presentation consists of perinatal onset of neurological symptoms, or seizures, or reduced movement at 24 to 48 hours post birth with verification on cranial ultrasound and/or Magnetic Resonance Imaging (MRI) of the presence of an asymmetric brain lesion. Specific imaging protocols may be needed for diagnosis in the early phases, such as diffusion MRI to identify an acute stroke in the first hours or days.207 In a delayed presentation, the infant may have an initially uncomplicated perinatal course and may not show signs of stroke or asymmetric brain injury until three to seven months of age, when unilateral weakness and early hand preference start to manifest.60,208

The current most predictive tools for early diagnosis of CP are a combination of brain magnetic resonance imaging (MRI) at term and a Prechtl’s Assessment of General Movements (GMs) in the fidgety period at 12 weeks post-term; 150 Specifically, GMs at one month and three months post-term age are highly associated with white matter abnormalities on MRI at term age.150 The GMs is a well
validated and reliable tool, and is more sensitive at predicting CP than other motor assessments used in infancy.\textsuperscript{73,150} The GMs is also useful for prediction of minor motor difficulties.\textsuperscript{211} Neuromotor assessments (such as the GMs) utilised in the neonatal period (< 4 months post-term) have strong validity to detect CP in infants born preterm, when correlated with criterion assessments at 12 months corrected age such as the BSID III; \textsuperscript{73} Although abnormalities in general movements are likely to be evident during the early writhing period (<6-9 weeks post-term) and the fidgety period (9-20 weeks post-term), asymmetries are only visible during the fidgety period.\textsuperscript{83,110,212} Asymmetries in fidgety GMs around 12 weeks post-term can be the first definitive clinical sign of hemiplegia.\textsuperscript{83,110,212}

Very early detection of hemiparesis frequently requires serial evaluation of subtle signs of interlimb differences or asymmetries in upper limb reaching (both spontaneous and purposeful), and grasp strength.\textsuperscript{109} Both bimanual and unimanual reaching with early strong hand preference at four to six months of age can be considered to be a strong sign of early hemiplegia.\textsuperscript{60} Studies of infants who have sustained an early perinatal stroke before four to seven months corrected age have suggested that until reach to grasp behaviours have emerged, an asymmetry may not be clearly evident and hemiparesis not confirmed.\textsuperscript{186,187}

Early intervention for infants at risk of developing congenital hemiplegia is considered to be very important, however, standard rehabilitation programs generally commence after six months of age due to delayed detection. A further consideration regarding the timing of commencement of intervention is that important phases of brain reorganisation may have already occurred.\textsuperscript{60,74}

Current approaches to rehabilitation in congenital hemiplegia in infants focus on toy presentation and sensory stimulation of the limb to encourage spontaneous reaching and grasping, however, the challenge is to obtain active movement from the impaired limb. A new approach utilising action observation to stimulate the mirror neuron system offers another opportunity to stimulate the damaged motor cortex before the infant has achieved volitional reach and grasp.

**Theoretical Framework**

The Mirror Neuron System (MNS) is comprised of 'mirror neurons'; specialised neurons which fire when one observes another performing an action and when one executes the action, facilitating understanding of the action and subsequent imitation of that action.\textsuperscript{79-81} Mirror neurons were discovered initially in the
premotor area (F5) of macaque monkeys and have since been identified in the rostral area of the inferior parietal lobule (PF) and the ventral premotor cortex. Direct evidence for the MNS in humans is lacking and there have been no studies published which have recorded single neurons from the proposed MNS in humans.

There is a growing body of neurophysiological and brain-imaging studies providing indirect evidence for the existence of the MNS in humans. Transcranial Magnetic Stimulation (TMS) studies have concluded that the MNS exists in humans and it differs to the MNS in monkeys. Non-purposeful and intransitive actions activate mirror neurons in humans and not in monkeys. When humans observe actions, the temporal features of cortical excitability suggest that the MNS codes for the whole action as well as the individual movements that comprise the action. In contrast, only the whole action is coded by the MNS in monkeys. These unique properties of the MNS in humans suggest that humans' capacity to imitate others' actions is related to the MNS.

Several studies have identified two cortical areas which correspond to motor function and are activated during action observation in humans; (i) the rostral area of the PF; and (ii) the lower area of the precental gyrus combined with the posterior area of the inferior frontal gyrus (IFG). It has been suggested that activation of mirror neurons located in the IFG (otherwise known as Broca’s area) in humans corresponds to activation of mirror neurons located in the PF in monkeys. In humans, the two mirror areas receive afferent input from the superior temporal sulcus (involved in processing motion), and send efferent input to the motor cortex.

The functional role of the MNS in both monkeys and humans has been proposed to underlie the processes of imitation and understanding the actions of others in relation to oneself. Demonstration of the MNS soon after birth introduces a new perspective to the treatment of infants with congenital brain injury. Emerging evidence from the basic sciences in infant rhesus macaque monkeys suggests that the immature MNS can facilitate the imitative capabilities of infants; and that consistent demonstration of imitative skills and subsequent manual skills can predict later motor development.
Sensorimotor reorganisation after early brain injury

It is well known that brain injuries impacting on the sensorimotor (SM) system may manifest in varying degrees of functional impairment, the extent of which is related to the size and site of the lesion, as well as the type of adaptive reorganisation that follows. The main mechanism for a reconnection of the motor cortex to the spinal cord consists of reorganisation within the damaged hemisphere, based on partial sparing of the primary motor cortex (i.e. ipsilesional reorganisation). When the lesion occurs at an early stage of development, a different mechanism can also be observed, whereby a significant number of monosynaptic fast-conducting ipsilateral motor projections (from the undamaged hemisphere) persist. Such projections are normally withdrawn within the first months of life. This alternative mechanism results in the undamaged hemisphere directly controlling both upper limbs, which is a pattern of reorganisation unknown to adult pathology (i.e. contralesional reorganisation).  

Emerging evidence in humans suggests that the pattern of SM reorganisation after early brain injury is determined during the first year of life, and possibly within the first few months. As children with reorganisation occurring in the damaged hemisphere (which results in the undamaged hemisphere directly controlling both upper limbs) have suboptimal upper limb motor activity, this pattern appears to be maladaptive. It has been suggested that the MNS may influence cortical reorganisation associated with upper limb impairment, and could potentially be a target of very early intervention.

Action Observation and Imitation

The process of observing an action (i.e. action observation) leads to activation of the MNS and stimulates the corticospinal system (motor pathways) prior to imitating the action. When the motor cortex is damaged (e.g. congenital brain lesion), action observation and imitation may influence cortical reorganisation by directly restoring the damaged motor pathways or reinforcing other pathways that originally helped to perform motor actions, or both.

In animal and human adult studies, action observation appears to activate the MNS and enhance excitability of the SM cortex. These findings suggest that the effects of an asymmetric brain lesion may be ameliorated by an infant-friendly and novel upper limb rehabilitation program based on action observation. The training program would aim to stimulate the damaged motor pathways from the lesioned
hemisphere to the impaired upper limb, which may subsequently improve later upper limb motor activity by changing the cortical reorganisation typically seen after this type of injury.

**Currently available therapeutic options and limitations**

Various interventions are used for improving upper limb motor function and reducing activity limitations for children with UCP. A recent systematic review was conducted which evaluated all upper limb interventions for infants (< 3 years) with brain injury. The interventions identified included: Constraint-Induced Movement Therapy (classic CIMT or modified for a paediatric population mCIMT); intramuscular Botulinum toxin A injections (BoNT-A) as an adjunct to occupational therapy (OT); forced-use therapy (FUT); and neurodevelopmental treatment (NDT) with or without upper limb casting.

The authors concluded that current evidence for very early upper limb interventions suggested small effects on unimanual capacity, bimanual coordination and self-care skills; however, there is limited data on the safety and the neural mechanisms underlying activity changes in response to these interventions. Further research is required to investigate the efficacy of upper limb interventions of this at-risk population at preschool age (< 3 years) and address the lack of attention to safety implications for infants.

**Proposed intervention and justification: why UP-BEAT?**

Action observation therapy is a novel upper limb rehabilitation approach based on the recent discovery of mirror neurons. This approach has been shown to effectively improve upper limb motor function in adult patients with chronic stroke. Action Observation Therapy is currently being investigated in a population of school-aged children (5–15 years) with UCP.

Action Observation Therapy has not yet been investigated in a randomised clinical trial for a population of infants with congenital brain lesion. The efficacy, benefits and safety implications of this novel rehabilitation for this at-risk population are unknown. Ideally, such an intervention should begin soon after the brain injury has occurred. It is difficult, however, to achieve voluntary activation of the motor cortex during the first weeks of life, as voluntary reaching is absent or immature. The activation of the motor cortex related to action observation may represent a unique opportunity for therapeutic intervention in this early period of development. As soon as voluntary reaching can be reliability elicited, very early intervention should be
supplemented with standard rehabilitative approaches aimed at encouraging symmetrical reach and grasp behaviours, as well as use of the limb in developing mobility.

In adults with stroke, action observation has been shown to effectively increase cortical excitability of the SM cortex and improve upper limb motor outcomes. Based on the hypothesis that the same activation can be elicited in infants, we predict that Action Observation Training will enhance the excitability of the SM cortex, accelerate the maturation of the corticospinal tract and the shaping of spinal motor circuits leading to better spontaneous use of the impaired upper limb. This could prevent the development of asymmetric reach and grasp in young infants with early asymmetric brain lesions.

Studies of early development of infants at risk of progressing to cerebral palsy, such as infants born preterm, frequently include a healthy term born reference group to take account of typical development progression. As there is very limited data on early imitation skills of infants or very early development of reaching and grasping in both term born and preterm infants a parallel healthy term born clinical trial is planned. As the provision of Action Observation Training and Toy Observation Training in the developmental period of 9-18 weeks post term are considered to be low risk and developmentally appropriate training approaches there is no risk but potentially some additional benefit for all infants. Inclusion of a cohort of healthy term born infants in parallel randomised comparison trial will provide a typically developing comparison of training approaches to our RCT of infants with asymmetric brain lesions.

**Broad aim of proposed study**

The broad aim of this study is to evaluate in two parallel randomised controlled trials with an identical sham control, whether the novel intervention Action Observation Training (AOT) is more effective than standard Toy Observation Training (TOT) in: (i) influencing the early development of reaching and grasping of typically developing infants (n=40), and ii) improving the upper limb motor activity of infants with asymmetric brain lesions (n=32).

**Methods**

Two randomised controlled trials (RCTs) with an identical sham control will be conducted to evaluate the efficacy of AOT compared to standard TOT in: (a) typically developing infants with a gestational age between 38 and 41 weeks at time of
recruitment (n=40); and (b) infants with asymmetric brain lesions aged 0 to 9 post-term weeks at time of recruitment (n=32).

This study will involve an at-risk population of infants (i.e. infants with asymmetric brain lesions). It would therefore be unethical to give no intervention to this population in the control arm. Standard TOT is the sham control intervention that will be used for both RCTs. It is similar to standard therapy as it involves the parents presenting toys to infants and encouraging spontaneous visual exploration, without demonstrating how to play with the toys. It does not include the active AOT component of the intervention for the treatment group.

The specific hypotheses to be tested are:

1. Typically developing infants receiving AOT will have faster development of reaching and grasping in both upper limbs, compared with infants receiving standard TOT;
2. Infants with asymmetric brain lesions receiving AOT will have faster development and greater quality and quantity of reaching and grasping in both upper limbs, compared with infants receiving standard TOT;
3. For both infant cohorts, AOT will result in greater equalisation of corticomotor pathways and retention of cortical reorganisation, compared with standard TOT;
4. Individual differences among infants in quality of general movements and imitative behaviour will modulate the effects of training on their development of reaching and grasping.

These hypotheses will address the following specific aims:

To determine if typically developing infants undergoing AOT will develop reaching and grasping earlier than those undergoing standard TOT. AOT is a novel upper limb training program based on action observation. Evidence suggests that action observation can activate the motor cortex and reinforce the corticospinal network. We will determine through an RCT if a 4-week AOT program (from 9 to 13 post-term weeks’ age) will influence the short-term outcomes of reaching and grasping, compared to a standard TOT program whereby action observation is replaced with toy observation (no grasping action demonstrated).

To determine if infants with asymmetric brain lesions undergoing AOT will develop reaching and grasping earlier, and have greater quality and quantity of reaching and grasping, compared to those undergoing standard TOT. Recent
studies suggest that an early therapeutic intervention in infants with asymmetric brain injury should aim to activate the impaired motor cortex. We will determine through an RCT if a 4-week AOT program (from 9 to 13 post-term weeks’ age) will lead to cortical activation associated with action observation and influence the development of reaching and grasping in these infants and improve their short- and long-term outcomes. AOT will again be compared with standard TOT. If we can show that this novel, very early intervention can improve short-term and long-term upper limb motor activity in infants with asymmetric brain lesions, this will guide clinical practice and enable more efficient allocation of therapy resources in the future.

To determine if AOT will lead to greater equalisation of corticomotor pathways and cortical reorganisation. We will determine if the 4-week AOT program will result in modified cortical coherence related to action observation through an electroencephalogram (EEG). If we can show that this novel very early intervention can lead to greater equalisation of cortical motor pathways and retention of cortical motor reorganisation, this will guide clinical practice with implications for other patients (infants with bilateral/symmetric brain injury, school-aged children with UCP, children with stroke). An understanding of the nature and timing of the brain lesion may indicate which infants respond better.

To determine if the individual differences among infants in quality of general movements and imitative behaviour will modulate the effects of training on their development of reaching and grasping. We will investigate these using standardised measures of spontaneous motility and imitation skills in both cohorts pre- and post-training. If we find these correlations, we can explore the possibility of individually tailoring very early therapeutic interventions.

Assessments will be performed at 9, 12, 14, 16 and 18 weeks. Follow-up will be performed at 6 and 12 months following intervention, to determine retention of effects. The timing of assessments coincides with early critical periods of spontaneous general movements and early imitation behaviours (9 weeks); period of fidgety movements (12 weeks); early symmetrical reaching (14–16 weeks) and symmetrical reaching to the midline (18 weeks) with criterion assessment on norm referenced measures at 6, 8 and 12 months corrected age. The experimental design and outcome measures are depicted on the CONSORT Flow chart in Figure 9.2.1.
The Human Research Ethics Committees at the Royal Children’s Hospital, Brisbane (HREC/09/QRCH/134), The University of Queensland (2009001870), The Royal Brisbane & Women’s Hospital (HREC/09/QRCH/134), The Mater Children’s Hospital and The Mater Mother’s Hospital (1814MC), the Stella Maris Scientific Institute and University of Pisa in Italy have granted approval for the study (43/2011).

**Study sample and recruitment**

Infants and their families will be recruited within a 50-200 km radius from The Royal Children’s Hospital, Brisbane, Australia. The recruitment process will target major metropolitan health districts across southeast Queensland, with the expectation that the cohort I sample will be representative of typically developing infants and the cohort II sample will be representative of infants with asymmetric brain lesions from Queensland.

Recruitment has been expanded to cover a 200 km radius from the Royal Brisbane and Women’s Hospital in Brisbane which includes three additional neonatal follow up teams at the Mater Mothers Hospital, Nambour Hospital and the Gold Coast Hospital in Queensland. All regional Paediatricians, Child Neurologists, Neonatologists, rehabilitation Physicians and Allied Health professionals (Occupational Therapists, Physiotherapists) have been informed of the study and referral processes. Similar strategies for achieving adequate participant enrolment have been adopted in the region of Tuscany, in Italy.

**Inclusion criteria**

*Cohort I: Typically Developing Infants (TDI) will include infants:*

1. With a gestational age at birth between 38 and 41 weeks;
2. Living within a 50 km radius of the Royal Children’s Hospital, Brisbane.

*Cohort II: Infants with asymmetric Brain Injury (aBI) will include infants:*

1. With an asymmetric (one sided or more involved on one side) or unilateral (one sided) brain injury (e.g. preterm or term arterial stroke, grade III or IV intraventricular haemorrhage, periventricular leukomalacia) identified on neonatal ultrasound or MRI;
2. Aged 0 to 9 post-term weeks at time of recruitment;
3. Living within a 200 km radius of the Royal Children’s Hospital, Brisbane.

A parallel clinical trial will admit infants with the same inclusion criteria into two parallel RCTs at the Stella Maris Scientific Institute in Pisa, Italy.
Exclusion criteria

Cohort I (TDI) will exclude infants:
With any post-natal medical complications (e.g. jaundice) requiring extended hospital admission or medical treatments.

Cohort II (aBI) will exclude infants:
With epileptic seizures unresponsive to treatment.

Sample size

Cohort I (TDI): Based on a 2-tailed t-test of 2 independent means, significance (alpha) level of 0.05, 80% power, predicted effect size of 0.8 and a 90% retention rate, we require 20 participants in each group (total sample of 40) for cohort I.

Cohort II (aBI): Sample size for cohort II was based on the assumption that the effect size of the proposed training will be similar to that found by Heathcock and colleagues in a population of preterm infants (n = 26) with a comparable training program, with a mean effect size of 2.4. Given the high effect size, the calculation returned a sample of only 4 participants per group, on a 2-tailed t-test, significance (alpha) level of 0.05 and 80% power. As our cohort II population will consist of two sub-groups of lesion type (i.e. arterial stroke and venous infarction) and will be highly variable with the presence of asymmetric brain injury; we have quadrupled the sample. We require 16 participants in each group (total sample of 32) for cohort II.

Randomisation

The allocation sequence will be comprised of computer-generated random numbers in a blocked design. Infants will be randomised to receive either Action Observation Training (AOT) or standard Toy Observation Training (TOT), from concealed envelopes opened by non-study personnel. Treatment allocation will be recorded on a piece of folded paper inside each envelope in random order (computer generated). The randomisation process will involve allocating a code to each infant, which consists of the letter ‘B’ or ‘G’ according to gender and a number based on date of birth (e.g. “B1”, “B2” and “G1”, “G2”). The infant’s name and code will be written on the paper inside the envelope and sealed. The envelope will be marked that it has been allocated and the infant’s code will be written on the front of the envelope. As each infant is entered, he/she will be allocated the next consecutive envelope, which will be opened by the non-study personnel who will read and record the treatment allocation from the paper inside the envelope. The randomisation
envelopes will be held and administered by the therapist providing training of the interventions for the parents.

**Blinding**

The therapists who will be training the parents in the interventions and the parents will be informed of group allocation; the therapists conducting the assessments will be masked to group allocation; and study personnel who will be assessing the outcomes will also be masked to group allocation. Randomised group allocation will remain concealed to the therapists who conducted the assessments until all data for the entire sample has been analysed.

**Study treatments**

Both cohorts will receive the same dosage of three 5-minute sessions (15 minutes per day) for 6 days per week, for 4 weeks. The total dosage of intervention will be 6 hours, over a period of 28 days. After baseline screening and randomisation, infants will receive either AOT or standard TOT.

Parents will be trained by an occupational therapist for approximately 30 minutes, and will be directly observed performing the training activities with the infant during training. Two follow-up phone calls regarding questions on how to perform the training will be addressed over the telephone with the therapist who trained the parents. Parents will be asked to video-record the sessions each day. Parents of the AOT group will repeatedly show the infant a grasping action on a set of three toys, presented in random order. Parents of the TOT group will show the infant the same set of three toys, also presented in random order, without the grasping action. The toys are mostly cylindrical in shape and vary in appearance, colour and patterns (i.e. cow, clown and musical instrument). Groups will be compared at 14, 16 and 18 weeks, as well as 6 months and 12 months following intervention.

To optimise comfort and convenience for their families, intervention training for parents, delivery of intervention and all assessments from 9 to 18 weeks will be performed in the infants’ home environment. To optimise the infant’s engagement in the interventions, parents will be advised to: (a) perform the training when the infant is calm and alert; (b) wiggle their fingers to engage the infant’s attention prior to commencing the training; and (c) stop the training, allow the infant to play briefly with the toys if the infant becomes distracted or stops attending to the parent’s hand and toy, before continuing the training.
Therapy protocols and delivery

Several occupational therapists will plan and conduct both intervention groups. These core therapists will be responsible for liaising with the parents to organise home visits to train the parents in their allocated interventions and for each set of assessments at 9, 12, 14, 16, 18 weeks corrected age (CA). The core therapists will also be responsible for organising the 6 and 12 month follow-up assessments at the Royal Children’s Hospital, Brisbane. Two other occupational therapists will provide training and follow-up phone calls for the parents.

An online diary that will only be accessible to the core therapists will be completed after each training session, follow-up phone call, home visit and follow-up assessment to summarise each activity for each infant. Any issues of concern such as difficulties with training and adverse events will be considered when data is analysed, as potential factors that may account for differences between cohorts. Video footage of each training and assessment session will be qualitatively and/or quantitatively analysed to assess treatment fidelity.

The core investigator team (RB, JZ, AG, KP, LF, MP) will meet regularly to review the progress of training and assessments for both cohorts, and will decide when any modifications to the protocol are required. The alternate training program (AOT, TOT) is standardised and would not be modified during the intervention period from 9-18 weeks post term. There is no expectation scientifically for discontinuing or modifying either the AOT or TOT, as there is no evidence to support one method over the other. Any additional interventions (motor training by Physiotherapists, Occupational Therapists will be monitored including the dose, focus and content of concomitant training), medications (for epilepsy) will be recorded at the next home visit and accounted for in secondary analysis. Parents in either study will be free to discontinue the training and exit the study if they wish and there would be no impact on their access to additional medical and allied health services.

Outcome measures and procedures

At 14, 16 and 18 weeks post-term or CA, quantity and quality of reaching and grasping will be measured using the Grasping and Reaching Assessment of Brisbane (GRAB); symmetry of reaching and grasping will be measured using the Hand Assessment of Infants (HAI); and pressure of grasping for each hand with a customised pressure sensor. At six months, the primary outcome measures will be the HAI and the Bayley Scales of Infant and Toddler Development (third edition;
BSID III), to measure cognitive and motor development. At eight months, the HAI will be used as well as electroencephalogram, to measure brain activity and cortical coherence. At 12 months, the primary outcome measures will again be the HAI and the BSID III.

1. Grasping and Reaching Assessment of Brisbane (GRAB)

This is the primary outcome measure of the study, developed by the research team. The GRAB will be performed at 14, 16 and 18 weeks post-term. Typically developing infants in Western cultures have been observed to acquire the important motor skills of reaching between three to five months of age and grasping as early as 18 weeks. Prior to reach onset, infants have been observed to demonstrate pre-reaching movements. These movements provide infants with multimodal input about their upper limb function within their environment, and provide sensorimotor experiences that can help infants to learn how to control their upper limbs.

Infants will be secured in a Baby Björn Babysitter Balance infant chair, allowing full range of motion of the arms. They will be presented with a toy at shoulder height at 75% of arm length for six trials of 30 seconds each, in the midline. Three different toys will be used in the various trials, in random order, to maintain the infant’s interest in the task. A video camera will be placed to the midline at approximately 1.2 metres above the infant to ensure a full view of the infant, his/her upper limbs and the toy. The video-recordings will be edited into fragments in which the infant is manipulating the toys, and will be analysed by researchers who are masked to group allocations. The following variables will be assessed: (1) number of hand-toy contacts, (2) hand-toy contact type, (3) hand-toy contact duration with visual attention, (4) hand-toy contact duration without visual attention, and (5) number of bilateral interactions. As the GRAB has been developed by our team, we propose to establish validity and reliability (intra-rater, inter-rater and test-retest). See Figure 9.2.2. for a schematic drawing of the GRAB set up.

2. Pressure of Grasping (GP)

Infants will be secured in the same infant chair used in the GRAB. They will be presented with a small customised pressure sensor in the form of a cylindrically shaped toy that allows recording of differential positive pressure. A soft foam strap is attached to the pressure sensor to secure the infants’ hand. Pressure will be continuously sampled at a minimum rate of 20 Hz and stored on a PC compatible
computer for further analysis. Each hand will be approached separately, using the pressure sensor. One trial for each hand will be performed, in a random order. The recording will begin as soon as the infant grasps the pressure sensor will continue for 120 seconds, unless the infant drops it. In that case, the trial will be repeated. The assessment will be video-recorded, synchronising the images with the activity of the pressure sensor. Grasp pressure will be assessed by the time series of positive hand pressure (expressed in Volts) corresponding to the selected video fragments will be analysed. The measures extracted will be: (1) maximum pressure, (2) minimum pressure, and (3) variance.

3. **Hand Assessment of Infants (HAI)**

   The HAI is a new assessment tool which aims to quantify hand function from two to eight months post-term. It will be performed at 14, 16 and 18 weeks, and again at six months post-term age. The scale was developed at the Karolinska Institute of Stockholm (Sweden; Prof Eliasson and Prof Sundholm) in collaboration with the University of Pisa. It is currently at the phase of standardisation in a normal population. The assessment is based on a video-recorded play session, which should be completed in approximately ten minutes. Upper limb movements, reaching and grasping will be elicited by presenting the infants with toys. The toys are designed to promote exploration and handling and are presented in various places (e.g. both sides, midline, close to the baby and at a distance) on multiple occasions, both from the assessor’s hand and, when possible, on the table. The scale consists of 40 items and includes both unimanual and bimanual tasks. Video recordings will be assessed by a researcher who is masked to group allocations.

4. **Prechtl’s Assessment of General Movements (GMs)**

   The assessment of GMs based on Prechtl’s method of observation is largely used as a diagnostic tool for neurological evaluation of the newborn and the young infant. The GMs has shown a high predictive value for neurodevelopmental outcome at 12 to 24 months for at-risk infants (e.g. brain lesion, CP, preterm); sensitivity is ≥ 92% and specificity is ≥ 82%, p < 0.01. The GMs has greater sensitivity in predicting CP than other motor assessments used in infancy. It involves assessing the quality of spontaneous motility using a short video-recording. Video-recordings will be performed at 9, 12, 14, 16 and 18 weeks CA. Video recordings will be performed for five minutes and then one additional minute to focus on each hand. The video-camera will be positioned in the midline approximately one
metre above the infant, at an angle of 45°. Infants will be recorded during while the
infant is in a calm, alert state at inter-feeding time, in a supine position and clothed
with wrists and ankles exposed. The analysis of the GMs will be performed by one of
the certified GMs assessors participating to the study, masked to group allocations.
5. Assessment of Imitation (AI)

All infants will be tested for simple gestural and vocal imitation on two
separate occasions, pre- and post-training, at nine and 12 weeks post-term age. This
assessment will determine whether individual infants have a reliable imitative
response, which may be important in interpreting the intervention results, as
individual differences between infants are expected. The nine week time point occurs
prior to the intervention; the 12 week time point occurs one week prior to completion
of the intervention. These time points have been specifically selected to determine:
(i) infants who are strong imitators; (ii) gestures reliably imitated; and (iii) whether the
imitative responses have been influenced by the intervention.

Infants will be assessed on the gestures most commonly reported in neonatal
imitation literature: (a) four facial gestures: tongue poking, mouth opening,
happy and sad emotional expressions; (b) two manual gestures: opening and closing
of the hand (grasping action) and index finger pointing; and (c) two vocal gestures:
“EEE,” “OOO”, as well as tongue clicks. The order of presentation for the gestures
will be randomised across infants. The assessment will be video-recorded.

A trained coder, masked to group allocations for the entire duration of the
study, will score imitation from the videotapes. The coder will view footage of the
infants’ behaviour during the assessment, and record frequencies for each of the
gestures listed above. These frequencies will be interpreted relative to the gestures
that were modelled. Imitation is evident when infants’ production of a gesture is
significantly greater in response to a matching gesture, than to any other gesture.
6. Bayley Scales of Infant and Toddler Development (third edition; BSID III)

The BSID III will be performed at six and 12 months corrected age. These
time points were chosen as: (a) reaching and grasping are expected to be
established by 6 months of age; (b) bimanual manipulation is expected to be
established by 12 months of age. The BSID III will be used to assess cognitive and
motor development. It is a frequently used standardized developmental assessment
throughout Australia; however its clinical utility in various populations of children has
not yet been established. It will consist of a series of simple interactions with the infant and will take between 50 and 80 minutes to administer.

Mean reliability coefficients were: 0.91 (Cognitive composite scale), 0.86 (Fine Motor subtest), 0.91 (Gross Motor subtest). Corrected correlation coefficients for test-retest reliability were: 0.67 (Fine Motor subtest, 2 to 4 months) and 0.83 (Gross Motor subtest, 33 to 42 months). Correlation between the BSID III Cognitive composite score and BSID II Mental Index score was 0.60; correlation between BSID III and II Motor composite scores was also 0.60. High correlations were found between the Wechsler Preschool and Primary Scale of Intelligence (third edition) Verbal, Performance and Full-Scale scores and the BSID III Cognitive score (0.72 – 0.79). Moderate correlations were found between the BSID III Motor composite and the Peabody Developmental Motor Skills (second edition) Motor quotients (0.49 – 0.57).

7. Electroencephalogram (EEG)

This test will be performed at eight months post-term and will last approximately 25 minutes. EEG is a standard method used in infants to measure brain activity and will be used in this study to explore possible brain functional correlates of motor development. EEG demonstrates mu rhythm suppression, which is considered to be a possible index of mirror neuron activity during observation and execution of hand actions. We will use a certified advanced system extensively used in infant testing, known as the Geodesic Sensor Net. It consists of a high-density net, which is applied in a few seconds.

We have tested modifications of mu rhythm using independent component analysis (ICA) of high-density EEG recordings, according to the paradigm used by Nyström and colleagues. ICA is a blind source separation technique that aims to find components that are most statistically independent of each other. The mu rhythm is expected to decompose into one or a few components from each subject and these are the only components useful for the analysis. We will have three different conditions for the infants to perform, from which mu rhythm activation will be estimated: (1) observe a static human model (baseline); (2) move his/her hand by reaching for and grasping an object (goal-directed action); and (3) move his/her hand by placing it on the table (non-goal-directed action). The difference in mu rhythm activation between the baseline and the two movement conditions will be used for
the selection of EEG sources and the difference between the two movement conditions will be analysed.

**Analyses**

Analyses will be conducted on an intention-to-treat basis using STATA 11. Data from each outcome measure will be summarised for each treatment group and descriptive statistics (frequencies, means, medians, 95% confidence intervals) calculated dependent on data distribution. A significance level of 0.05 will be used. The effects of action observation training on development of reaching and grasping (Hypotheses 1 to 3) will be explored by a two-way repeated-measures analysis of variance (ANOVA) for parametric variables, including duration of hand-toy contact, maximum and minimum pressure, and pressure variance. Correction for multiple comparisons will be applied. The Kruskal-Wallis statistic will be used for non-parametric measures, including the number of hand-toy contact and the HAI score. To test the possible influence of GMs quality and imitative behaviour (Hypothesis 4), these will be considered as covariates in a multifactorial analysis. The results of EEG signal analysis will be compared between the two groups of each cohort using parametric tests. Post hoc analyses will be undertaken to investigate clinical characteristics of infants who have a greater response to either intervention.

**Discussion**

This paper outlines the background and design for two parallel randomised controlled trials with an identical sham control, comparing Action Observation Training (AOT) with standard Toy Observation Training (TOT) to: (a) influence the early development of reaching and grasping of typically developing infants, and (b) improve the upper limb motor activity of infants with asymmetric brain lesions. To our knowledge this study is the first to directly compare the two approaches for this population. Furthermore, we will be establishing validity and reliability for the newly developed outcome measures.
Figure 9.2.1. Flow chart of UP-BEAT study according to CONSORT guidelines
Figure 9.2.2. Schematic drawing of the setting for the Grasp and Reach Assessment of Brisbane

a) Camera
b) Toy presented on a stick
c) Screen
d) Slightly reclined infant chair (40°)
9.3. Stages of development of the scoring criteria and methods of the Grasp and Reach Assessment of Brisbane
**Development of scoring criteria and procedures (Stages 1 to 5)**

*Stage 1.*

The Grasp and Reach Assessment of Brisbane (GRAB) video-recordings were originally scored using a hard-copy scoring sheet, with separate columns to record when an outcome was observed to commence. Outcomes recorded on the sheet were: (i) duration of time (in frames out of a total possible 700 frames per video-clip) that the infant contacted the toy; and (ii) noting whether a contact was ‘palmar’ or ‘dorsal’ based on hand orientation during toy contact.

Following pilot scoring of the videos for 3 healthy participants, it was discussed in the research team that each UL should be scored separately and that the scoring sheet be revised to reflect this; and that recording the infant’s visual attention and/or lack of visual attention would be another important outcome to consider, and could help to explain reduced UL activity.

*Stage 2.*

The hard-copy scoring sheet was revised to include separate columns for each UL, and separate columns to record when an outcome was observed to commence and cease. Two new outcomes were added, and all unimanual outcomes recorded on the sheet for each UL were: (i) duration of time (in frames out of a total possible 700 frames per video-clip) that the infant contacted the toy; (ii) noting whether a contact was ‘palmar’ or ‘dorsal’ based on hand orientation during toy contact; (iii) duration of visual attention (VA, when the infant was looking at the toy); and (iv) duration of no VA (when the infant was not looking at the toy).

Following pilot scoring of the videos for 6 healthy participants, the following concerns/questions were raised:

- Should toy contacts that were therapist-initiated when the infant was not attending to the task be classified as a toy contact?
- Should toy contacts that appeared to be accidental (e.g. infant grasps toy with one hand and then releases the toy abruptly, which results in the toy being flung onto the other hand) be classified as a toy contact?
- Difficulty determining visual attention from the videos on occasion (e.g. if the camera lens is aimed at the top of the infant’s head and it is difficult to view the infant’s eyes)
Classifying a toy contact as palmar or dorsal does not capture if the hand is open or closed as well during contact and could be an important indicator of differences between ULs or groups (e.g. infants with asymBI may demonstrate less palmar contacts as well as more dorsal open or closed contacts compared to healthy infants)

Should toy contacts that involve brief contacts and releases close to the toy, while hand orientation changes be classified as separate contacts or a continuous contact?

After discussions with the research team, it was decided that:

- Therapist-initiated toy contacts were not to be included as toy contacts
- Accidental contacts were to be included but noted as ‘accidental’ with a brief explanation
- Occasions when visual attention was difficult to capture were to be noted as such with a brief explanation, and the camera set-up standardised to capture the infant’s vision during the task
- Making note of open/closed orientations in addition to palmar/dorsal orientations during toy contact
- Classifying several brief contacts and releases with changing hand orientation as continuous when hand distance from toy is approximately less than 1cm and the infant continues to contact and release the toy in a similar manner over a prolonged period of time.

It was also discussed that a graphical representation of the GRAB outcomes would be a more suitable way to understand and present the data, which led to the third revision.

**Stage 3.**

The hard-copy scoring sheet was replaced by an electronic scoresheet using Microsoft Excel, and the rater was required to draw coloured lines on the scoresheet using the computer mouse, to indicate when a unimanual outcome was observed to commence and cease. Some outcomes were revised and more were added, with each unimanual outcome measured as a duration of time (in frames out of a total possible 700 frames per video-clip). Unimanual outcomes were also categorised into ‘activity’ (toy contact only) or ‘interaction’ (visual attention/no visual attention with/without toy contact) to incorporate visual attention. A blue coloured line
represented ‘left UL activity’ and a green coloured line represented ‘right UL activity’; while a purple coloured line represented ‘interaction by both ULs’, such that each spreadsheet would depict a graphical representation of unimanual activity and interaction for each video-clip, for each participant.

The following ‘activity’ outcomes were recorded: (1) no toy contact (NT); (2) ‘palmar open’ toy contact (Po, toy contact with a palmar open-handed orientation); (3) ‘palmar closed’ toy contact (Pc, toy contact with a palmar closed-handed orientation); (4) ‘dorsal open’ toy contact (Do, toy contact with a dorsal open-handed orientation); and (5) ‘dorsal closed’ toy contact (Dc, toy contact with a dorsal and closed-handed orientation). The following ‘interaction’ outcomes were recorded: (1) no interaction (NI, infant was not looking or contacting toy); (2) VA (V); (3) VA with toy contact (V+T); (4) toy contact without VA (T). Definitions for each outcome were discussed until a consensus was met by the research team. Refer to Table 3 for the GRAB scoring criteria with definitions (versions 1 and 2).

Following pilot scoring of 3 healthy participants using this revised scoring procedure raised some concerns. Firstly, the procedure was time-consuming, with scoring time ranging from 1 to 3 hours for a 3-minute video. Secondly, it was predicted that infants with asymBI would demonstrate less palmar toy contacts than the healthy infants as a palmar hand orientation during toy contact would be indicative of a more mature developing grasp. It was then discussed that ‘palmar’ toy contact could include both open-handed and close-handed orientations based on hand orientation approaching and contacting the toy. Thirdly, it was discussed that the scoring of the GRAB needed to be quantitative rather than qualitative, and would therefore require a more sophisticated method to record, collate and analyse the outcomes for each infant.

Stage 4.

The electronic graphical scoresheet using Microsoft Excel was replaced by an electronic spreadsheet using Microsoft Excel, which required the rater to enter a numerical code that represented an outcome for each UL, for each of the 700 frames per video-clip.

Recorded ‘activity’ outcomes were the same as those outlined previously in Stage 3, except for ‘palmar’ contacts: (1) no toy contact (NT); (2) ‘palmar’ toy contact (P, toy contact with a palmar open-handed or closed-handed orientation); (3) ‘dorsal open’ toy contact (Do, toy contact with a dorsal open-handed orientation); and (4)
‘dorsal closed’ toy contact (Dc, toy contact with a dorsal and closed-handed orientation). Recorded ‘interaction’ outcomes were the same as those outlined previously in Stage 3: (1) no interaction (NI, infant was not looking or contacting toy); (2) VA (V); (3) VA with toy contact (V+T); (4) toy contact without VA (T). Definitions for each outcome were discussed until a consensus was met by the research team.

The software program Matlab v.R2011a was selected to collate the data recorded by the rater from all time points for each participant, as well as obtaining additional outcomes which were then summarised into another Microsoft Excel spreadsheet. The advantages of using Matlab were: (i) ability to collate and analyse data from multiple Excel spreadsheets simultaneously using a Matlab-encoded script; (ii) ability to summarise data in different ways including graphs; and (iii) ability to obtain additional outcomes based on the original data, using a Matlab-encoded script. Additional outcomes obtained using Matlab were:

- Unimanual activity outcomes per UL: (5) number of palmar contacts; (6) number of dorsal open contacts; and (7) number of dorsal closed contacts.
- Unimanual interaction outcomes (in duration of time as seconds out of a total possible 180 seconds) per UL: (5) duration of no interaction; (6) duration of visual attention; (7) duration of visual attention with toy contact; and (8) toy contact without visual attention.
- Bilateral interaction outcomes: (1) number of occasions of bilateral toy contact with VA; and (2) number of occasions with bilateral toy contact without VA.

The Microsoft Excel spreadsheet was used to calculate the following from these additional outcomes: (i) number of total contacts per UL; (ii) duration (in seconds) of bilateral contact with VA; (iii) mean contact time per contact with VA; (iv) mean contact time per contact without VA; (v) time delay before contacting toy with VA per UL; and (v) time delay before contacting toy without VA. Duration of each unimanual interaction outcome was also calculated as a percentage of total video time (approximately 180 seconds/ three minutes); and number of each unimanual activity outcome was calculated as a percentage of total contacts demonstrated by both ULs in one video-clip. Matlab was also used to analyse the data recorded by the rater and summarise the output, as a method to compare rater calculations using Microsoft Excel, with Matlab calculations generated by a Matlab encoded script.
Following pilot scoring of 15 randomly selected video-recordings using this revised scoring procedure raised a number of concerns. Firstly, the procedure was significantly time-consuming, with scoring time ranging from 1 to 4 hours for a 3-minute video. Secondly, classifying/interpreting whether a toy contact was ‘palmar’ open/closed or ‘dorsal’ open/closed was potentially subjective and difficult at times, particularly if: (i) the quality of video-recordings are reduced; (ii) the infant’s hands were only partially open/closed; (iii) the infant’s hand/finger orientation around the toy was partially palmar and partially dorsal; and (iv) the infant’s wrist or arm is contacting the toy rather than the hand or fingers. It was suggested that: (i) Matlab could instead calculate whether a toy contact occurs for each UL with or without visual attention, or to consider visual attention as a separate outcome to a toy contact; (ii) hand orientation (palmar/dorsal and open/closed) be removed so that the rater is just required to record the presence or absence of a toy contact; or included in a secondary analysis of the videos, and only if the infant has demonstrated toy contacts as hand orientation cannot be analysed if the infant does not demonstrate toy contacts at all. Some issues were also raised related to technical difficulties associated with Matlab due to coding errors, errors in calculations when a specific outcome was not observed in a video, and moderate to large differences found in GRAB outcomes when comparing rater scores with Matlab scores. When difficulties with Matlab arose, assistance was sought from Clinical Motion Analysis consultants, whose available time was limited.

After discussions with the research team, it was decided that: (i) the scoring procedure needed to be simplified yet more sophisticated than using a Microsoft Excel spreadsheet; (ii) the outcomes measured on the GRAB needed to be more quantitative ‘behaviours’ that reflected developmental progression of unimanual reaching to grasping; and (iii) that Matlab was too problematic a program to use without the assistance of specialists to troubleshoot and fix errors as they arose; and needed to be replaced by a program that was easier to use.

Stage 5.

The electronic Microsoft Excel spreadsheet was replaced by the free annotation software BEST v.2012+ to record GRAB outcomes. The BEST software enabled the rater to: (i) assign each outcome to a computer keyboard key and record data straight from the video-recordings; (ii) export the data into a Microsoft Excel spreadsheet; and (iii) easily convert the duration of each outcome from frames into
seconds using a simple calculation. Scores from each video-clip, for each infant, were then collated into a Microsoft Excel spreadsheet. Unimanual outcomes were measured for each UL either as a duration of time (in frames out of a total possible 700 frames per video-clip), which was converted into seconds; or a number of observed events. Outcomes were revised again, as well as definitions that were discussed until a consensus was met by the research team. A unimanual contact was defined as “any hand contact initiated by the infant with any part of the toy”; whereas a unimanual grasp was defined as “grasping the toy using all or most fingers with the palm, and closing around the toy – briefly or for a prolonged period of time”.

Outcomes (duration of time in frames or number of observed events) were categorised to measure ‘detection of asymmetry between hands’ or ‘early reach to grasp development for each hand’:

- Detection of asymmetry between hands: (i) VA without toy contact; (ii) VA with toy contact; (iii) number of midline toy contacts; and (iv) duration of midline toy contacts with visual attention.
- Early reach to grasp development for each hand: (0) no activity; (1) prehensile movements; (2) transport phase; (3) reach and toy contacts; (4) toy grasps; (5) toy manipulation; and (6) other activity.

Following pilot scoring of 4 randomly selected infants, the following observations were raised:

- There were very few clear examples of ‘manipulation’ were observed – the toys were attached to sticks and were not easy to manipulate within the hand; rather, what was often observed were changes in hand orientation or hand movements around the toys
- There were difficulties on occasion with classifying a behaviour as ‘no activity’ or ‘other activity’ – with the main points of difference including whether the infant’s UL was static or mostly static; if UL movement was directed towards or away from the toys; and if release of the toys after contact was brief or prolonged
- There were occasions when an infant contacted the toys without reaching (e.g. UL was at the midline and contacted the toy with small movements, or used swiping movements with the hand/fingers rather than the whole arm).
The BEST software was difficult to use when an infant demonstrate several behaviours over a short period of time, and could not accurately capture when behaviours overlapped between ULs or bimanual behaviours. Following further discussions with the research team, revision 6 (final revision) was made, which also involved seeking another software program that could accommodate coding of several behaviours over a short period of time, and would enable the rater to analyse unimanual as well as bimanual outcomes.
9.4. Ethics approval – Queensland Children’s Health Services Human Research Ethics Committee
CHILDREN’S HEALTH SERVICES

DISTRICT MANAGEMENT

1 July 2010

Dr Andrea Guzzetta
Queensland Cerebral palsy and Rehabilitation Research Centre
Level 1 Surgical Building
ROYAL CHILDREN’S HOSPITAL

Dear Dr Guzzetta

Re: The effect of infant action observation training on the early development of hand reaching and grasping in healthy infants with early brain injury

I am pleased to advise that the above project was approved by the Royal Children’s Hospital Executive on 1 July 2010.

Sincerely

Linda Hardy
Chief Operating Officer
Royal Children’s Hospital
Children’s Health Services
QUEENSLAND CHILDREN'S HEALTH SERVICES DISTRICT (RCH) ETHICS COMMITTEE

Professor John Petrie (Chair) 3355 3323
Mas Amanda Smith (Co-ordinator) 3636 9167

Dr Andrea Guzzetta
Queensland Cerebral Palsy and Rehabilitation Research Centre
Royal Children's Hospital
Herston Road
Herston QLD 4029

Dear Dr Guzzetta,

HREC Reference number: HREC/09/QRCH/134

Thank you for submitting the above project for ethical review. This project was first considered by the QLD Children's Health Services District (RCH) Human Research Ethics Committee (HREC) held on the 9th December 2009. Many thanks for Professor Boyd for attending the meeting to answer any queries the Committee had in relation to the project.

This HREC is constituted and operates in accordance with the National Health and Medical Research Council's (NHMRC) National Statement on Ethical Conduct in Human Research (2007), NHMRC and Universities Australia Australian Code for the Responsible Conduct of Research (2007) and the CPMP/IChE Note for Guidance on Good Clinical Practice. Attached is the HREC Composition with specialty and affiliation with the Hospital (Attachment 1).

I am pleased to advise that the Human Research Ethics Committee has granted approval of this research project. The documents reviewed and approved include:

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Please note the following conditions of approval:

1. We require an annual progress report (or sooner if the project is completed) concerning the study. This must include progress to date or outcome in the case of completed research. (In accordance with National Statement 5.5.3)

2. In accordance with the National Statement (3.3.12), before beginning the clinical phase of the research, researchers should register clinical trials in a publicly accessible domain.

3. If the project does not proceed, the Committee must be informed as soon as possible. (In accordance with National Statement 5.5.6)

4. The Committee must be informed of any potential or realised problem with bioethical implications, if such occurs during the conduct of the research project.

5. Any serious adverse event (SAE) that arises in the context of this research, or involving a researcher conducting this research, must be reported to the Ethics Committee within 72 hours and reported to the sponsor (if applicable) within the stipulated time frame.

Serious Adverse Event Reports that are generated off-site may be (a) Serious Unexpected Adverse Reactions or (b) Serious Events which the Research Team believes cannot be related to the research intervention. The Research team must report incidents of (a) during multi-centre trials. Such are required to be submitted to the Chair of the QLD Children’s Health Services District Ethics Committee (RCH) on receipt by the researcher. A summary of the SAE reports is to accompany the submission. Information required includes: patient details (age & sex), adverse event, outcome and the likelihood of the event being related to the study drug/device/procedure.

With respect to all SAEs, the researcher must provide his or her opinion as to whether the SAE is directly related to the research Intervention. A copy of the SAE Summary must be provided. (This can be obtained from the Ethics Officer)

6. Amendments to the research project which may affect the ongoing ethical acceptability of a project must be submitted to the HREC for review. Major amendments should be reflected in a revised online NEAF (accompanied by all relevant updated documentation and a cover letter from the principal investigator, providing a brief description of the changes, the rationale for the changes, and their implications for the ongoing conduct of the study). Hard copies of the revised NEAF, the cover letter and all relevant updated documents with tracked changes must also be submitted to the HREC coordinator as per standard HREC SOP. Further advice on submitting amendments is available from:


7. The Ethics Committee will conduct a randomly identified audit of a proportion of research projects approved by the Committee. That audit process will look at such issues as;
   a. Security of Documents
   b. Consent Form Register
   c. Serious Adverse Events Register
   d. Withdrawal of Participants — who and why
   e. The de-identification of data

8. We require researchers to give a declaration of intention to publish their findings in a refereed journal or similar peer-reviewed forum. Your work must be in accordance with the following:

   - National Statement on Ethical Conduct in Human Research:
   - Queensland Health Management Research Policy:
   - Joint NHMRC / AVCC Statement and Guidelines on Research Practice (1997):
   - Declaration of Helsinki:

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Guidelines under Section 95 of the Privacy Act 1995 and Guidelines approved under Section 95A of the Privacy Act 1995.

Queensland Health Privacy Guidelines IS42 & IS42A:

9. Researchers should note, if not QLD Health employees, a Blue Card may be required for contact with children.

Should you have any queries about the HREC’s consideration of your project please contact Amanda Smith (Coordinator) or Professor John Pearn (Chairperson). The HREC terms of Reference, Standard Operating Procedures, membership and standard forms are available from:

You are reminded that this letter constitutes ethical approval only. You must not commence this research project at a site until separate authorisation from the District CEO or Delegate of that site has been obtained.

A copy of this approval must be submitted to the District Executive with a completed Institutional Approval Form for authorisation from the CEO or Delegate to conduct this research within the Children’s Health Service District.

The HREC wishes you every success in your research.

With kind regards,

[Signature]

Professor John Pearn
Chair
Queensland Children’s Health Services District Ethics Committee (RCH)

Cc: Ethics Committee Files
Members of the Ethics Committee
Children's Health Services District
Ethics Committee
2009

Professor John Pearn (Chair)
National Statement 5.1.30 a – Institute Affiliation
Chairperson

Mrs. Susan Geissler
National Statement 5.1.30 c – Institute Affiliation
Knowledge of, and current experience in, the professional care, counselling or
treatment of people

Professor Keith Grimwood
National Statement 5.1.30 f – Institute Affiliation
Current research experience that is relevant to research proposals to be
considered

Dr Stephen Haigh
National Statement 5.1.30 b – No Institute Affiliation
Layperson

Dr Honey Heussler
National Statement 5.1.30 f – No Institute Affiliation
Current research experience that is relevant to research proposals to be
considered

Professor Alan Isles
National Statement 5.1.30 f – Institute Affiliation
Current research experience that is relevant to research proposals to be
considered

Professor Roy Kimble
National Statement 5.1.30 f – Institute Affiliation
Current research experience that is relevant to research proposals to be
considered

Mr Hugh Miller
National Statement 5.1.30 f – Institute Affiliation
Current research experience that is relevant to research proposals to be
considered

Associate Professor James Nixon
National Statement 5.1.30 b – No Institute Affiliation
Social Worker and Medical Researcher

Mrs. Paula Penfold
National Statement 5.1.30 b – No Institute Affiliation
Layperson

Dr Jan Pratt
National Statement 5.1.30 c – Institute Affiliation
Knowledge of, and current experience in, the professional care, counselling or
treatment of people

The Reverend Bob Rogers
National Statement 5.1.30 d – No Institute Affiliation
Pastoral Care role in the community

Mrs Amanda Smith
Ethics Co-ordinator

Mr. David Watt
National Statement 5.1.30 c – No Institute Affiliation
Lawyer

This HREC is constituted and operates in accordance with the National Health and Medical Research Council’s (NHMRC) National
Statement on Ethical Conduct in Human Research (2007), NHMRC and Universities Australia Australian Code for the Responsible
Conduct of Research (2007) and the CPMP/ICH Note for Guidance on Good Clinical Practice.

Amanda Smith
Co-ordinator
Children's Health Services District Ethics Committee
8 December 2009

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ROYAL CHILDREN'S HOSPITAL & HEALTH SERVICE DISTRICT
INSTITUTIONAL APPROVAL FOR RESEARCH

Title of Research Project: The effect of infant action observation training on the early development of hand reaching and grasping in healthy infants and in infants with early brain injury.

Chief Investigators: RCH

Dr Andrea Guzzetta (Signed)

Brief explanation of the relevance to RCH & HSD in the context of our Mission Statement:
This project will explore the effects of interventions performed before the age of 3 months in infants with asymmetrical brain damage at risk for cerebral palsy. Two types of intervention will be compared in our study. The first one is called Action Observation Training. It consists of daily sessions in which one of the parents of the baby shows him/her some hand actions (grasping) performed on a toy, and then gives the toy to the baby to manipulate. The second one is called Toy Observation Training. It consists of daily sessions in which one of the parents of the baby shows him/her a toy, and then gives it to the baby to manipulate. The Action Observation Training will encourage the baby to focus on the action of the hand. This can promote the development of appropriate hand actions by imitation. The Toy Observation Training will encourage the baby to focus on the characteristics of the object. This can promote the development of appropriate hand actions by selection of the movements based on the characteristics of the toy.

As part of the same project, a cohort of 40 healthy term infants will be assessed with the same protocol.

The Executive requires an outline of the infrastructure cost implications of the research to the RCH & HSD. Please outline any such costs under the following categories (append if more space required).

<table>
<thead>
<tr>
<th>STAFF TIME:</th>
<th>Medical</th>
<th>Medical and Allied Health staff may refer appropriate families to this study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nursing</td>
<td>Nil.............................................................................................................</td>
</tr>
<tr>
<td></td>
<td>Allied Health</td>
<td>Medical and Allied Health staff may refer appropriate families to this study</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>Nil.............................................................................................................</td>
</tr>
</tbody>
</table>

| EQUIPMENT: | Research (Capital) | Nil............................................................................................................. |
|           | Research (Maintenance) | Nil............................................................................................................. |
|           | *Service (Capital) | Nil............................................................................................................. |
|           | *Service (Maintenance) | Nil............................................................................................................. |
|           | Consumables (Clinical) | Nil............................................................................................................. |
|           | Consumables (Clerical) | Nil............................................................................................................. |

Other Costs: All costs will be covered by study funding

How do you propose that these infrastructure costs be funded?

Head of Department (The above information is correct and I am prepared to take financial responsibility for the project).

Certification by Head of Dept. I certify that I am prepared to have the project carried out in my Department, and will not be requiring undocumented support from the RCH & DHS.

*Service is to include RSL/CHS/CYMHS

To be signed by Manager Finance if approved.

Signature: ___________________________ Name: ___________________________ Date: __________/________/______
QLD CHILDREN'S HEALTH SERVICES (RCH)
HUMAN RESEARCH ETHICS COMMITTEE

Associate Professor Roslyn Boyd
Queensland Cerebral Palsy and Rehabilitation Research Centre
Royal Children's Hospital
Herston Road
Herston QLD 4029

Dear Professor Boyd,

HREC Reference number: HREC/09/QRCH/134
Amendment number: HREC/09/QRCH/134/AM3
Amendment Date: 25 February 2011

Many thanks for your letter of the 25th February regarding an Amendment for the above project. I am pleased to advise that the amended documents reviewed and approved at the meeting were:

<table>
<thead>
<tr>
<th>Document</th>
<th>Version</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protocol</td>
<td>2</td>
<td>25 February 2011</td>
</tr>
<tr>
<td>Parent/Guardian Information Sheet and Consent Form - PGIS Asymmetrical Brain Injury</td>
<td>2.0</td>
<td>25 February 2011</td>
</tr>
<tr>
<td>Notification of amendment</td>
<td></td>
<td>25 February 2011</td>
</tr>
<tr>
<td>Covering Letter</td>
<td></td>
<td>25 February 2011</td>
</tr>
<tr>
<td>Parent/Guardian Information Sheet and Consent Form – PGIS Healthy Term Infants</td>
<td>2.0</td>
<td>25 February 2011</td>
</tr>
</tbody>
</table>

The QLD Children’s Health Services (RCH) Human Research Ethics Committee (HREC) is constituted and operates in accordance with the National Health and Medical Research Council’s “National Statement on Ethical Conduct in Human Research (2007); NHMRC and Universities Australia Australian Code for the Responsible Conduct of Research (2007) and the “CPMP/ICH Note for Guidance on Good Clinical Practice”.

It should be noted that all requirements of the original approval still apply.

Yours sincerely,

[Signature]

Professor John Pean
Chair
Queensland Children’s Health Services (RCH) Human Research Ethics Committee

Cc: Ethics Committee Files
QLD CHILDREN’S HEALTH SERVICES (RCH)  
HUMAN RESEARCH ETHICS COMMITTEE

Professor John Pearn  (Chair) 3365 5323  
Mrs Amanda Smith (Co-ordinator) 3636 9167

Associate Professor Roslyn Boyd  
Scientific Director  
Queensland Cerebral Palsy and Rehabilitation Research Centre  
Royal Brisbane & Women’s Hospital  
Level 7, Block 6  
Herston QLD 4029

Dear Professor Boyd,

**HREC Reference number: HREC/09/QRCH/134**  
**Project title: The effect of infant action observation training on the early development of hand reaching and grasping in healthy and in infants with early brain injury.**  
**Amendment number: HREC/09/QRCH/134/AM04**  
**Amendment Date: 09 November 2011**

Many thanks for your letter of the 9th November regarding an amendment to the above study. These have now been reviewed. I am pleased to advise that the amended documents reviewed and approved were:

<table>
<thead>
<tr>
<th>Document</th>
<th>Version</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Covering Letter</td>
<td></td>
<td>09 November 2011</td>
</tr>
<tr>
<td>Notification of amendment</td>
<td></td>
<td>09 November 2011</td>
</tr>
<tr>
<td>Protocol</td>
<td>3</td>
<td>09 November 2011</td>
</tr>
<tr>
<td>Parent/guardian Information Sheet and Consent Form</td>
<td>3.0</td>
<td>09 November 2011</td>
</tr>
<tr>
<td>Study Flyers</td>
<td>3.0</td>
<td>09 November 2011</td>
</tr>
</tbody>
</table>

The QLD Children’s Health Services (RCH) Human Research Ethics Committee (HREC) is constituted and operates in accordance with the National Health and Medical Research Council’s “National Statement on Ethical Conduct in Human Research (2007), NHMRC and Universities Australia Australian Code for the Responsible Conduct of Research (2007) and the “CPMP/ICH Note for Guidance on Good Clinical Practice”.

A copy of this letter must be forwarded to the Research Governance Officer. It should be noted that all requirements of the original approval still apply.

Yours sincerely,

Professor John Pearn  
Chair  
Queensland Children’s Health Services (RCH) Human Research Ethics Committee

Cc: Ethics Committee Files
QLD CHILDREN’S HEALTH SERVICES (RCH)  
HUMAN RESEARCH ETHICS COMMITTEE

Professor John Pearn (Chair) 3365 5323  
Mrs Amanda Smith (Co-ordinator) 3636 9167

Level 3, RCH Foundation Building  
Royal Children’s Hospital  
Herston QLD 4029 Australia  
Telephone (07) 3636 9167  
Facsimile (07) 3365 5455

8th February 2012

Associate Professor Roslyn Boyd  
Scientific Director  
QLD Cerebral Palsy & Rehabilitation Research Centre  
Royal Brisbane & Women’s Hospital  
Level 7, Block 6  
Herston QLD 4029

Dear Professor Boyd,

HREC Reference number: HREC/09/QRCH/134  
Amendment number: HREC/09/QRCH/134/AM05

Many thanks for your letter of the 7th February regarding an amendment to the above project. The Committee notes that due to difficulties in recruitment, the project will now be a multicentre trial. This has been reviewed. I am pleased to advise that the amended documents reviewed and approved at the meeting were:

<table>
<thead>
<tr>
<th>Document</th>
<th>Version</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Notification of amendment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Covering Letter</td>
<td></td>
<td>7th February 2012</td>
</tr>
</tbody>
</table>

This project has Ethics approval for the following sites:

- Royal Children’s Hospital, Brisbane
- Nambour Hospital
- Caboolture Hospital
- Logan Hospital
- Gold Coast Hospital
- Redcliffe Hospital
- Ipswich Hospital

The QLD Children’s Health Services (RCH) Human Research Ethics Committee (HREC) is constituted and operates in accordance with the National Health and Medical Research Council’s “National Statement on Ethical Conduct in Human Research (2007), NHMRC and Universities Australia Australian Code for the Responsible Conduct of Research (2007) and the “CPMP/ICH Note for Guidance on Good Clinical Practice”.

You are reminded that this letter constitutes ethical approval only. You must not commence this research project at a site until separate authorisation from the District CEO or Delegate of that site has been obtained.

A copy of this approval must be submitted to the Research Governance Officer for authorisation from the CEO or Delegate to conduct this research within the Children’s Health Service District.

It should be noted that all requirements of the original approval still apply.

Yours sincerely,

Micah Perez - Thesis Appendices

For - Professor John Pearn  
Chair  
Queensland Children’s Health Services (RCH) Human Research Ethics Committee  
Cc: Ethics Committee Files
Professor Roslyn Boyd  
Scientific Director  
Queensland Cerebral Palsy & Rehabilitation Research Centre  
Level 7, Block 6  
Royal Brisbane and Women’s Hospital  
Herston, QLD 4029

Dear Professor Boyd,

HREC Reference number: HREC/09/QRCH/134  
Amendment number: HREC/09/QRCH/134/AM07

Many thanks for your letter of the 10th December regarding an amendment for the above study. This has now been reviewed and I am pleased to advise that the amended documents reviewed and approved were:

<table>
<thead>
<tr>
<th>Document</th>
<th>Version</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Covering Letter</td>
<td></td>
<td>10 December 2012</td>
</tr>
<tr>
<td>Application</td>
<td>AU/1CDDF05</td>
<td></td>
</tr>
<tr>
<td>PGIS &amp; Forms for both cohorts</td>
<td>3</td>
<td>06 November 2012</td>
</tr>
<tr>
<td>Protocol</td>
<td>4</td>
<td>06 November 2012</td>
</tr>
<tr>
<td>Study Flyer – combined cohort &amp; asymmetric brain injury cohort versions</td>
<td></td>
<td>06 November 2012</td>
</tr>
<tr>
<td>Referral Form</td>
<td></td>
<td>06 November 2012</td>
</tr>
<tr>
<td>Referral Flyer – asymmetric brain injury cohort</td>
<td></td>
<td>06 November 2012</td>
</tr>
<tr>
<td>Parent Contact General Information form</td>
<td></td>
<td>06 November 2012</td>
</tr>
<tr>
<td>Assessment &amp; Treatment Schedule for parents</td>
<td></td>
<td>06 November 2012</td>
</tr>
<tr>
<td>Video Consent Form</td>
<td></td>
<td>06 November 2012</td>
</tr>
</tbody>
</table>

The QLD Children’s Health Services (RCH) Human Research Ethics Committee (HREC) is constituted and operates in accordance with the National Health and Medical Research Council’s “National Statement on Ethical Conduct in Human Research (2007), NHMRC and Universities Australia Australian Code for the Responsible Conduct of Research (2007) and the “CPMP/ICH Note for Guidance on Good Clinical Practice”.

The Committee also gives approval for the addition of the Gold Coast Hospital as a site. A separate Site Specific Assessment application will need to be made to that site before research may commence.

A copy of this letter must be forwarded to the Research Governance Officer. It should be noted that all requirements of the original approval still apply.

Yours sincerely,

Professor John Pearn  
Chair  
Children’s Health Services Queensland Human Research Ethics Committee

Co: Ethics Committee Files

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CHILDREN'S HEALTH SERVICES QUEENSLAND
HUMAN RESEARCH ETHICS COMMITTEE

Professor John Pearn (Chair) 3365 5323
Mrs Amanda Smith (Co-ordinator) 3636 9167

Level 3, RCH Foundation Building
Royal Children's Hospital
Herston QLD 4029 Australia
Telephone (07) 3365 9167
Facsimile (07) 3365 5455

27th November 2013

Professor Roslyn Boyd
Scientific Director
Queensland Cerebral Palsy & Rehabilitation Research Centre
Level 7, Block 6
Royal Brisbane and Women's Hospital
Herston, QLD 4029

Dear Professor Boyd,

**HREC Reference number: HREC/09/QRCH/134**
Amendment number: HREC/09/QRCH/134/AM09

Many thanks for your letter of the 20th November regarding an amendment to the above project. This has now been reviewed and the Committee is happy to give approval this extra measure.

It should be noted that all requirements of the original approval still apply.

Yours sincerely,

[Signature]

Professor John Pearn
Chair
Children's Health Services Queensland Human Research Ethics Committee

Cc: Ethics Committee Files
9.5. Ethics approval – The University of Queensland Behavioural & Social Sciences Ethical Review Committee
THE UNIVERSITY OF QUEENSLAND
Institutional Approval Form For Experiments On Humans
Including Behavioural Research

Chief Investigator: Dr Andrea Guzzetta, A/Prof Roslyn Boyd, A/Prof Virginia Slaughter, Prof Paul Colditz, Miss Imogen Fisher

Project Title: The Effect Of Infant Action Observation Training On the Early Development Of Hand Reaching And Grasping In Healthy And In Infants With Early Brain Injury

Supervisor: None

Co-Investigator(s) Mrs Kerry Provan, A/Prof Thomas Suddendorf, Dr Mark Nielsen, Ms Janine Oostenbroek, Mrs Lisa Finlay, Dr Lynne McKinnay, Dr Kate Sinclair, A/Prof Stephen Rose, Dr Maria Giulia D’Acunto, Dr Koa Whittingham

Department(s): Queensland Cerebral Palsy Rehabilitation and Research Centre, Royal Children’s Hospital, School of Medicine

Project Number: 2009001870

Granting Agency/Degree: QCMRI Program Grant; 2 Queensland Health Research Grants

Duration: 31st December 2011

Comments:
Expedited review on the basis of approval from the Queensland Children’s Health Services District (RCH) HREC, approval dated 08/12/2009.

Name of responsible Committee:- Behavioural & Social Sciences Ethical Review Committee
This project complies with the provisions contained in the National Statement on Ethical Conduct In Human Research and complies with the regulations governing experimentation on humans.

Name of Ethics Committee representative:-
Dr Jack Broerse
Chairperson
Behavioural & Social Sciences Ethical Review Committee

Date 10/11/10 Signature
THE UNIVERSITY OF QUEENSLAND
Institutional Approval Form For Experiments On Humans
Including Behavioural Research

Chief Investigator: Dr Andrea Guzzetta, A/Prof Roslyn Boyd, A/Prof Virginia Slaughter, Prof Paul Colditz, Miss Imogen Fisher

Project Title: The Effect Of Infant Action Observation Training On the Early Development Of Hand Reaching And Grasping In Healthy And In Infants With Early Brain Injury

Supervisor: None

Co-Investigator(s) Mrs Kerry Provan, A/Prof Thomas Suddendorf, Dr Mark Nielsen, Ms Janine Oostenbroek, Mrs Lisa Findlay, Dr Lynne McKinlay, Dr Kate Sinclair, A/Prof Stephen Rose, Dr Maria Giulia D'Acunto, Dr Koa Whittingham

Department(s): Queensland Cerebral Palsy Rehabilitation and Research Centre, Royal Children's Hospital, School of Medicine

Project Number: 2009001870

Granting Agency/Degree: QCMRI Program Grant; 2 Queensland Health Research Grants

Duration: 31st December 2011

Comments:
Expedited review on the basis of approval from the Queensland Children's Health Services District (RCH) HREC, approval dated 08/12/2009.

Name of responsible Committee:-
Behavioural & Social Sciences Ethical Review Committee

This project complies with the provisions contained in the National Statement on Ethical Conduct in Human Research and complies with the regulations governing experimentation on humans.

Name of Ethics Committee representative:-
Dr Jack Broerse
Chairperson
Behavioural & Social Sciences Ethical Review Committee

Date 10/01/10 Signature
Additional Notes to Ethics Approval

1. The clearance number should be quoted on the protocol coversheet when applying to a granting agency and in any correspondence relating to ethical clearance.

2. Clearance will normally be for the duration of the project unless otherwise stated in the institutional clearance form.

3. Adverse reaction to treatment by subjects, injury, or any other incidents affecting the welfare and/or health of subjects attributable to the research should be promptly reported to the Head of School and the Ethics Committee.

4. Amendments to any part of the approved protocol (including change of Investigator/s), documents, or questionnaires attached to the clearance must be submitted to the Ethics Committee for approval.

5. Unforeseen events that might affect continued ethical acceptability of the project must be immediately reported to the Ethics Committee.

6. Discontinuation of the project before the expected date of completion must be reported to the Ethics Committee, giving reasons.

7. Advisers on 'Integrity in Research'
   As part of the University's commitment to the institutional statement, Code of conduct for the Ethical Practice of Research (1990), and the NHMRC's National Statement on Ethical Conduct in Research Involving Humans (2007), designated positions have been appointed as advisers on integrity in research. The Chairperson of each ethics committee acts in an advisory capacity to provide confidential advice on such matters as misconduct in research, the rights and duties of postgraduate supervisors, and procedures for dealing with allegations on research misconduct within the University. The contact number for the Chairperson of each ethics committee can be obtained from the Ethics Officer.

8. The Committee reserves the right to visit the research site and view materials at any time, and to conduct a full audit of the project.

9. It is the Committee's expectation, whenever possible, that work should result in publication. The Committee would require details to be submitted for our records.
10. Staff and students are encouraged to contact either the Ethics Officer (3365 3924), or Chairperson on other issues concerning the conduct of experimentation/research (e.g., involvement of children, informed consent) prior to commencement of the project and throughout the course of the study.
THE UNIVERSITY OF QUEENSLAND
Institutional Approval Form For Experiments On Humans
Including Behavioural Research

Chief Investigator: A/Prof Roslyn Boyd, A/Prof Virginia Slaughter, Prof Paul Colditz, Ms Imogen Fisher

Project Title: The Effect Of Infant Action Observation Training On the Early Development Of Hand Reaching And Grasping In Healthy And In Infants With Early Brain Injury - 11/03/2011 - AMENDMENT

Supervisor: A/Prof Roslyn Boyd, Prof Jenny Ziviani

Co-Investigator(s): Dr Andrea Guzzetta, Mrs Kerry Provan, A/Prof Thomas Suddendorf, Dr Mark Nielsen, Ms Janine Oostenbroek, Mrs Lisa Findlay, Dr Lynne McKinlay, Dr Kate Sinclair, A/Prof Stephen Rose, Dr Koa Whittingham, Mica Perez, Dr Iona Novak, Prof Jenny Ziviani

Department(s): Queensland Cerebral Palsy Rehabilitation and Research Centre, Royal Children's Hospital, School of Medicine

Project Number: 2009001870

Granting Agency/Degree: QCMRI Program Grant; 2 Queensland Health Research Grants

Duration: 31st December 2011

Comments:

Name of responsible Committee:-
Behavioural & Social Sciences Ethical Review Committee
This project complies with the provisions contained in the National Statement on Ethical Conduct in Human Research and complies with the regulations governing experimentation on humans.

Name of Ethics Committee representative:-
Associate Professor John McLean
Chairperson
Behavioural & Social Sciences Ethical Review Committee

Date 18/03/2011 Signature

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# THE UNIVERSITY OF QUEENSLAND

Institutional Approval Form For Experiments On Humans
Including Behavioural Research

<table>
<thead>
<tr>
<th><strong>Chief Investigator:</strong></th>
<th>A/Prof Roslyn Boyd, A/Prof Virginia Slaughter, Prof Jenny Ziviani, Dr Andrea Guzzetta</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Project Title:</strong></td>
<td>The Effect Of Infant Action Observation Training On the Early Development Of Hand Reaching And Grasping In Healthy And In Infants With Early Brain Injury - 14/11/2011 - AMENDMENT</td>
</tr>
<tr>
<td><strong>Supervisor:</strong></td>
<td>A/Prof Roslyn Boyd, Prof Jenny Ziviani</td>
</tr>
<tr>
<td><strong>Co-Investigator(s):</strong></td>
<td>Prof Paul Colditz, Mrs Kerry Provan, A/Prof Thomas Suddendorf, Dr Mark Nielsen, Ms Janine Oostenbroek, Mrs Lisa Findlay, Dr Lynne McKinlay, Dr Kate Sinclair, A/Prof Stephen Rose, Dr Koa Whittingham, Micah Perez, Ms Imogen Fisher</td>
</tr>
<tr>
<td><strong>Department(s):</strong></td>
<td>Queensland Cerebral Palsy Rehabilitation and Research Centre, Royal Children's Hospital, School of Medicine</td>
</tr>
<tr>
<td><strong>Project Number:</strong></td>
<td>2009001870</td>
</tr>
<tr>
<td><strong>Granting Agency/Degree:</strong></td>
<td>Australian Research Council Discovery Grant</td>
</tr>
<tr>
<td><strong>Duration:</strong></td>
<td>31st December 2011</td>
</tr>
<tr>
<td><strong>Comments:</strong></td>
<td></td>
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</tbody>
</table>

**Name of responsible Committee:-**
**Behavioural & Social Sciences Ethical Review Committee**
This project complies with the provisions contained in the National Statement on Ethical Conduct in Human Research and complies with the regulations governing experimentation on humans.

**Name of Ethics Committee representative:-**
Associate Professor John McLean
Chairperson
Behavioural & Social Sciences Ethical Review Committee

Date 17/11/2011  Signature [Signature]
THE UNIVERSITY OF QUEENSLAND
Institutional Human Research Ethics Approval

Project Title: The Effect Of Infant Action Observation Training On the Early Development Of Hand Reaching And Grasping In Healthy And In Infants With Early Brain Injury - 19/12/2012 - AMENDMENT

Chief Investigator: Prof Roslyn Boyd, Prof Virginia Slaughter, Prof Jenny Ziviani, Dr Andrea Guzzetta

Supervisor: A/Prof Roslyn Boyd, Prof Jenny Ziviani

Co-Investigator(s): Prof Paul Colditz, Mrs Kerry Provan, Prof Thomas Suddendorf, Dr Mark Nielsen, Ms Janine Oostenbroek, Mrs Lisa Findlay, Dr Lynne McKinlay, Dr Kate Sinclair, A/Prof Stephen Rose, Dr Koa Whittingham, Ms Micah Perez, Ms Imogen Fisher, Ms Joanne Bowden, Dr Luke Jardine, A/Prof Michael O'Callaghan, Dr Peter Schmidt, Ms Claire Spellman, Mr Vincent van Dijk

School(s): Queensland Cerebral Palsy Rehabilitation and Research Centre, Royal Children's Hospital, School of Medicine

Approval Number: 2009001870

Granting Agency/Degree: Australian Research Council Discovery Grant

Duration: 31st December 2013

Comments:

Note: If this approval is for amendments to an already approved protocol for which a UQ Clinical Trials Protection/Insurance Form was originally submitted, then the researchers must directly notify the UQ Insurance Office of any changes to that Form and Participant Information Sheets & Consent Forms as a result of the amendments, before action.

Name of responsible Committee:
Behavioural & Social Sciences Ethical Review Committee
This project complies with the provisions contained in the National Statement on Ethical Conduct in Human Research and complies with the regulations governing experimentation on humans.

Name of Ethics Committee representative:
Associate Professor John McLean
Chairperson
Behavioural & Social Sciences Ethical Review Committee

Signature Date 20/12/2012
9.6. Ethics approval – The Royal Brisbane and Women’s Hospital
Dear Professor Colditz


Thank you for submitting an application for authorisation of the above research project. I am pleased to inform you that authorisation has been granted for this study to take place at the Royal Brisbane and Women's Hospital.

If you have any questions relating to this authorisation please contact the Research Support Officer on 3636 8579. In addition to the conditions of approval imposed by the Human Research Ethics Committee, you are required to submit any amendments to the Research Support Officer, as well as to the Human Research Ethics Committee. Amendments may include changes to the protocol, budget, information sheets, consent forms, clinical trial agreements and any other research-related documentation.

I wish you every success with your research.

Thank you for conducting this important research.

Yours sincerely

Dr David Alcorn
Executive Director

Professor Ian Jones
A/Executive Director
Royal Brisbane & Women's Hospital
PO Herston Qld 4029 Ph: 3636 1585
9.7. Ethics approval – Mater Health Services
Human Research Ethics Committee
MATER HEALTH SERVICES HUMAN RESEARCH ETHICS COMMITTEE

6th October 2011

A/Prof Rostyn Boyd
Qld Cerebral Palsy and Rehabilitation Research Centre
Royal Children's Hospital
Herston Road
Herston QLD 4029

Dear A/Prof Boyd

Re: Protocol Ref No. 1814MC – The effect of infant action observation training on the early development of hand reaching and grasping in healthy infants and in infants with early brain injury

I write to advise that the Mater Health Services Human Research Ethics Committee considers the above study to meet the requirements of the National Statement on Ethical Conduct in Human Research (2007) and has granted ethical approval for your research proposal. Please accept our very best wishes for the success of this study. In all future correspondence with the Committee please quote the Mater reference number.

Documents reviewed and approved include:

- NEAF cover sheet
- NEAF form – version 1, 14/03/2010 (original); version 2, 23/06/2011
- Study flyer – version 1, 14/03/2011
- Ethics approval from The University of Queensland Behavioural & Social Sciences Ethical Review Committee, 2009001870, 08/12/2009
- Amendment approval from The University of Queensland Behavioural & Social Sciences Ethical Review Committee, 2009001870, 11/03/2011
- Ethics approval from The Queensland Children’s Health Services District (RCH) Ethics Committee, HREC/09/QRCH/134, 08/12/2009
- Amendment approval from The Queensland Children’s Health Services District (RCH) Ethics Committee, HREC/09/QRCH/134/AM03, 25/02/2011
- Ethics approval from the Royal Brisbane and Women's Hospital Human Research Ethics Committee, HREC/09/QRCH/134, 20/04/2011
- Patient Information sheet – Master copy, version 2 28/08/2010; Site specific copy for Mater Mother's Hospital, version 1 20/05/2011; Site specific copy for Mater Children's Hospital, version 1 20/05/2011
- Consent Form – Master copy, version 2 25/03/2010; Site specific copy for Mater Mother's Hospital, version 1 20/05/2011; Site specific copy for Mater Children's Hospital, version 1 20/05/2011
- Staff Information sheet

This approval is valid until 6th October 2014. Please note the following conditions of approval.

- Any departure from the protocol detailed in your proposal must be reported immediately to the Committee.
• When you propose a change to an approved protocol, which you consider to be minor, you are required to submit a written request for approval to the Chairperson, through the Secretary. Such requests will be considered on a case by case basis and interim approval may be granted subject to ratification at the next meeting of the Committee.

• Where substantial changes to any approved protocol are proposed, you are required to submit a full, new proposal for consideration by the Human Research Ethics Committee.

• You are required to advise the Research Ethics Coordinator immediately of any complaints made, or expressions of concern raised, in relation to the study, or if any serious or unexpected adverse events occur.

• Under the NHMRC National Statement on Ethical Conduct in Research Involving Humans, research ethics committees are responsible for monitoring approved research to ensure continued compliance with ethical standards, and to determine the method of monitoring appropriate to each project. You are required to provide written reports on the progress of the approved project annually, the first report being due on 6th October 2012 and finally on completion of the project. (The Progress Report is located at [http://www.mater.org.au/Home/Research/Human-Research-Ethics-Committee.aspx](http://www.mater.org.au/Home/Research/Human-Research-Ethics-Committee.aspx) or can be accessed through the Mater Intranet, Applications, Research Register then under the project name or altimately can be emailed to you). Please inform the Committee of publications, presentations at Conferences, education and quality improvement outcomes from this study. The Committee may also choose to conduct an interim audit of your research.

• Please be aware that all study procedures including follow up of participants and data analysis should be completed within the approval time frame or an extension should be requested.

You are reminded that this letter constitutes ethical approval only. You must not commence this research project until authorisation from the Research Governance Office has been obtained.

Please contact the Executive Director in the participating hospital/hospitals prior to commencing of the study. To access medical records, for the purpose of this study, please provide a copy of this approval letter to the Corporate Health Information Manager. I would also be grateful if you could confirm the date of commencement. (All correspondence should be directed to the Mater Research Ethics Coordinator.)

Yours sincerely

[Signature]

A/Prof Andrew Crowden
Chairperson
Mater Health Services Human Research Ethics Committee
MATER HEALTH SERVICES HUMAN RESEARCH ETHICS COMMITTEE

17th December 2012

Professor Roslyn Boyd
Department of Paediatrics and Child Health
School of Medicine
University of Queensland
c/- Level 7 Block 6
Royal Brisbane & Women's Hospital
Herston
QUEENSLAND 4006

Dear Professor Boyd

Re: 1814MC. The effect of infant action observation training on the early development of hand reaching and grasping in healthy and in infants with early brain injury

I write to advise that the Mater Health Services Human Research Ethics Committee has granted ethical approval for the proposed amendments for the above study. Please note: a revised NEAF is not required to be submitted for amendment requests.

Documents reviewed and approved include:

<table>
<thead>
<tr>
<th>Document</th>
<th>Version</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Research Protocol</td>
<td>4</td>
<td>06/11/12</td>
</tr>
<tr>
<td>Proposed Budget</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PGIS form -- cohort 2 (MMH)</td>
<td>3</td>
<td>06/11/12</td>
</tr>
<tr>
<td>PGIS form -- cohort 2 (MCH)</td>
<td>3</td>
<td>06/11/12</td>
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<tr>
<td>Consent form -- cohort 2 (MMH)</td>
<td>3</td>
<td>06/11/12</td>
</tr>
<tr>
<td>Consent form -- cohort 2 (MCH)</td>
<td>3</td>
<td>06/11/12</td>
</tr>
<tr>
<td>Study Flyer -- cohort 2</td>
<td></td>
<td>06/11/12</td>
</tr>
<tr>
<td>Referral Form</td>
<td></td>
<td>06/11/12</td>
</tr>
<tr>
<td>Referral Flyer -- cohort 2</td>
<td></td>
<td>06/11/12</td>
</tr>
</tbody>
</table>

You are reminded that this letter constitutes ethical approval only. You may also need to consult with the Research Governance Office to ensure the amendments comply with the existing authorisation that has been obtained.

Please accept our best wishes for the remainder of the study and should you have any queries, please do not hesitate to contact the Research Ethics Secretariat on 3163 1585. In all future correspondence with the Committee please quote the Mater reference number.
Yours sincerely

[Signature]

A/Prof Andrew Crowden
Chairperson
Mater Health Services Human Research Ethics Committee
9.8. Ethics approval – Mater Health Services
Human Research Governance
MHS & MMRI Human Research Governance - SSA Authorisation

31st October, 2011

A/Prof Roslyn Boyd
Qld Cerebral Palsy and Rehabilitation Research Centre
Royal Children’s Hospital
Herston Road
Herston Qld 4029

Dear A/Prof Boyd

Re: HREC Protocol Ref No. 1814MC; SSA Ref No. 1814MC (RG). The effect of infant action observation training on the early development of hand reaching and grasping in healthy infants and in infants with early brain injury

Thank you for submitting an application for authorisation of this project. I am pleased to inform you that authorisation has been granted for this study to take place at the following site(s):

Mater Children’s Hospital
Mater Mother’s Hospital

The following conditions apply to this research proposal. These are additional to those conditions imposed by the Human Research Ethics Committee that granted ethical approval.

1. The Research Governance Officer must be informed of any problems that arise during the course of the study which may affect conduct of the study at the site.
2. Proposed amendments to the research protocol or conduct of the research which may affect the ethical acceptability of the project, and which are submitted to the HREC for review, are copied to the research governance officer;
3. Proposed amendments to the research protocol or conduct of the research which only affects the ongoing site acceptability of the project, are to be submitted to the research governance officer;
4. Proposed amendments to the research protocol or conduct of the research which may affect both the ongoing ethical acceptability of the project and the site acceptability of the project are to be submitted to the research governance officer after a HREC decision is made.

We wish you every success in undertaking this research.

Yours sincerely

Dr Louise Hutley, PhD
Research Governance Officer
Room 55, Lvl 3, Quarters Building
Mater Medical Research Institute
Raymond Terrace
South Brisbane Qld 4101

Ph: (07) 3163 8336
Fax: (07) 3163 1588
Email address: research.governance@mmri.mater.org.au
MHS & MMRI Human Research Governance - Amendment Outcome

13th February, 2013

Prof Roslyn Boyd
Scientific Director
Queensland Cerebral Palsy & Rehabilitation Research Centre
Royal Children's Hospital
Herston Rd
Herston Qld 4029

Dear Prof Boyd


Thank you for submission of a proposed amendment to the above project for post-authorisation consideration by the Research Governance Office. I am pleased to inform you that authorisation is granted for this study amendment to take place at the following site(s):

Mater Children's Hospital and Mater Mother's Hospital, South Brisbane

Documents reviewed and authorised include:

- Budget & Funding
- NEAF form, 07/11/12
- SSA form, 08/11/12
- PGIS and Consent forms for both cohorts – version 3, 06/11/12
- Site-specific PGIS and Consent forms for cohort 2 – version 2, 06/11/12
- Study Protocol – version 3, 10/08/11
- Study Protocol – version 4, 06/11/12
- Study Flyer for cohort 2, 06/11/12
- Site-specific Study Flyer for cohort 2, 29/11/12
- Referral Form – not dated
- Referral Flyer for cohort 2, 06/11/12
It should be noted that all conditions of the original Mater authorisation still apply.

Please accept our best wishes for the remainder of the study and should you have any queries please contact the Research Governance Officer on 3163 8836. Please quote the Mater Research Governance (SSA) reference number in all future correspondence.

Yours sincerely

Dr Louise Huttley, PhD
Senior Research Governance Officer
Room 55, Lvl 3, Quarters Building
Mater Medical Research Institute
Raymond Terrace
South Brisbane Qld 4101
Ph: (07) 3163 8336
Fax: (07) 3163 8588
Email address: research.govt@umm.mater.org.au
9.9. Ethics approval – Gold Coast Hospital and Health Service
District Research Governance
10 January 2013

Dr Peter Schmidt
Department of Paediatrics
Gold Coast Hospital
108 Nerang St
Southport, 4215

Dear Dr Schmidt

HREC reference number: HREC/09/QRCH/134
SSA reference number: SSA/12/QGC/203

Thank you for submitting an application for authorisation of this project. I am pleased to inform you that authorisation has been granted for this study to take place at the following site(s):

- Gold Coast Hospital and Health Service

The following conditions apply to this research proposal. These are additional to those conditions imposed by the Human Research Ethics Committee that granted ethical approval.

1. Proposed amendments to the research protocol or conduct of the research which may affect the ethical acceptability of the project are to be submitted to the HREC for review. A copy of the HREC approval/rejection letter must be submitted to the RGO;
2. Proposed amendments to the research protocol or conduct of the research which only affects the ongoing site acceptability of the project, are to be submitted to the research governance officer;
3. Proposed amendments to the research protocol or conduct of the research which may affect both the going ethical acceptability of the project and the site acceptability of the project are to be submitted firstly to the HREC for review and then to the research governance officer after a HREC decision is made.

Yours sincerely

[Signature]

for Jane Hancock
Acting Chief Operations Officer
District CEO or Delegate
Gold Coast Hospital and Health Service

[Signature]

Ian Pieper
Research Governance Officer
Gold Coast Hospital and Health Service
9.10. Ethics approval – Stella Maris Foundation (Italy)
FONDAZIONE STELLA MARIS
ISTITUTO DI RICOVERO E CURA A CARATTERE SCIENTIFICO PER LA
NEUROPSICHIAVRIA DELL'INFANZIA E DELL'ADOLESCENZA

Prot.n° 43/2011 Comitato Etico

Allegato seduta del Comitato Etico del 31 gennaio 2011

<table>
<thead>
<tr>
<th>Membri</th>
<th>Presente</th>
<th>Assente</th>
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</thead>
<tbody>
<tr>
<td>Prof. Bruno Grassi</td>
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<td>x</td>
</tr>
<tr>
<td>Prof. Renzo Guerrini</td>
<td></td>
<td></td>
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<tr>
<td>Prof. Pierantonio Macchia</td>
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</tr>
<tr>
<td>Prof. Paolo Moneta</td>
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<tr>
<td>Prof. Eugenio Ripepe</td>
<td></td>
<td>x</td>
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<tr>
<td>Mons. Raffaelle Schiavone</td>
<td></td>
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<tr>
<td>Dott. Giovanni Ferretti</td>
<td></td>
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<tr>
<td>Sig.ra Anna Paola Giglioli</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dott. Giuseppe De Vito</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Oggetto: Progetto di Ricerca “The effects of infant action observation training on the early development of hand reaching and grasping in healthy infants and in infants with asymmetrical brain damage”.

Responsabile: Dr. Andrea Guzzetta

Il Comitato Etico nella seduta del 31 Gennaio 2011 ha esaminato la seguente documentazione:

[x] Progetto in oggetto
[x] Consenso Informato

e ha successivamente espresso il seguente parere:

[x] Approvato
[ ] Approvato con nota
[ ] Non approvato per le motivazioni indicate
[ ] Sospesa in attesa dei chiarimenti richiesti

Note richieste:

Questo Comitato Etico è organizzato ed opera nel rispetto delle norme di buona pratica clinica (GCP-ICH) e della normativa vigente.

Calambrone, 31 gennaio 2011

Il Segretario/Verbalizzante
(Dr. Giovanni Ferretti)

Il Presidente del Comitato Etico
(Prof. Paolo Moneta)
9.11. Study documents – Study flyers
UP-BEAT STUDY

What is this study about? We want to know if simple training performed before 3 months of age can influence the development of grasping and reaching in infants. If we find that this new form of very early training has some effects on arm and hand skills, it may change the way we provide treatment in the future for children with brain injury.

How can you help? We need 40 healthy babies and 32 babies with asymmetric brain lesions. Babies in the study will be randomly assigned to one of two types of training.

What do you need to do? You will be taught a simple technique of showing toys to your baby and you will be asked to do this for 5 minutes, 3 times a day for 4 weeks. This will be during the period from 9 to 13 weeks of age and can be easily done at nappy change time. We will loan you a video camera to film these sessions. In addition to this daily training, we will need to assess your baby throughout their first year. Assessments at 9, 12, 14, 16 and 18 weeks of age consist of a short video (10-15 minutes) of your baby which we can do in your home. The final 2 assessments at 6 and 12 months take a little more time and will need to be done at the Royal Children’s Hospital. This will include an EEG at 6 months.

Benefits:
- the training may enhance your child’s reaching and grasping skills
- you will receive a summary report of your child’s assessment results
- you will be assisting us to gather information that may influence treatment for children with brain injury and provide better outcomes for their future

If you would like to find out more or know someone who might be interested, please contact:

Professor Roslyn Boyd (Principal Investigator)
mob: 0434 608 443 email: r.boyd@uq.edu.au

Micah Perez (PhD Student)
ph: 3646 5372 mob: 0418 122 544 email: m.perez1@uq.edu.au
What is this study about? We want to know if simple training performed before 3 months of age can influence the development of grasping and reaching in infants. If we find that this new form of very early training has some effects on arm and hand skills, it may change the way we provide treatment in the future for children with brain injury.

How can you help? We need 32 babies with early brain abnormalities (asymmetric brain lesions). Babies in the study will be randomly assigned to one of two types of training.

What do you need to do? You will be taught a simple technique of showing toys to your baby and you will be asked to do this for 5 minutes, 3 times a day for 4 weeks. This will be during the period from 9 to 13 weeks of age and can be easily done at nappy change time. We will loan you a video camera to film these sessions. In addition to this daily training, we will need to assess your baby throughout their first year. Assessments at 9, 12, 14, 16 and 18 weeks of age consist of a short video (10-15 minutes) of your baby which we can do in your home. The final 2 assessments at 6 and 12 months take a little more time and will need to be done at the Royal Children’s Hospital. This will include an EEG at 6 months.

Benefits: ● the training may enhance your child’s reaching and grasping skills
       ● you will receive a summary report of your child’s assessment results
       ● you will be assisting us to gather information that may influence treatment for children with brain injury and provide better outcomes for their future

If you would like to find out more or know someone who might be interested, please contact:
Professor Roslyn Boyd (Principal Investigator)
mob: 0434 608 443 email: r.boyd@uq.edu.au
Micah Perez (PhD Student)
ph: 3646 5372 mob: 0418 122 544 email: m.perez1@uq.edu.au
9.12. Study documents – Study referral forms
UP-BEAT

UPper Limb Baby Early Action Observation Training Study

What is this study about? Our study evaluates if a simple training technique that we can show parents, beginning at 9 weeks post-term age improves reaching and grasping development of infants with asymmetric brain lesions. Infants in the study will be randomly assigned to one of two types of training. All infants receive training and follow-up.

Inclusion criteria: We need 32 infants aged <9 weeks post-term with a unilateral (one side) or asymmetric (more involved on one side) brain lesion, identified on neonatal ultrasound or MRI:

- Unilateral or asymmetric preterm or term arterial stroke
- Unilateral or asymmetric grade III or IV intraventricular haemorrhage
- Unilateral or asymmetric periventricular leukomalacia.

Families of these infants should live within 200km of the Royal Children's Hospital so that they can be visited at home for assessments.

Exclusions: Infants with uncontrolled epileptic seizures (i.e. unresponsive to treatment).

What will you need to do?

- Identify potentially eligible infants who are aged <9 weeks post-term
- Ask the family if they are interested in learning more about the study.
- If interested, then refer the infant to one of our research team (contact details overleaf).

What will the families need to do? The parents of the infants will be taught a simple technique to train early hand skills that we will ask them to do for 5 minutes, 3 times a day for 4 weeks (beginning at 9 weeks post-term and ending at 13 weeks post-term). The training can easily be performed at each nappy change time. We will loan the family a video camera to film these sessions. In addition to this daily training, we will assess the infant at 9, 12, 14, 16 and 18 post-term weeks of age during a HOME VISIT. Each visit will involve a short video (10-15 minutes) of the infant.
**Benefits:**

- The training may enhance their child’s reaching and grasping skills in either group
- The family will receive a summary report of their child’s developmental assessment results.

**Contact Details:**
To find out more information or to refer a potentially eligible infant, please contact:

*Professor Roslyn Boyd (Principal Investigator)*
Direct line: 3365 5315  mob: 0434 608 443  email: r.boyd@uq.edu.au

*Micah Perez (PhD Student)*
ph: 3646 5372  mob: 0418 122 544  email: m.perez1@uq.edu.au

**UP-BEAT Study**

<table>
<thead>
<tr>
<th>Age (Wks PTA)</th>
<th>Assessment Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;9 WKS PTA</td>
<td>Recruitment: All eligible families &lt;9 weeks post-term, with unilateral or asymmetric brain lesions (arterial stroke or venous infarction only) on neonatal ultrasound or MRI, with no epileptic seizures unresponsive to treatment approached. N=32</td>
</tr>
<tr>
<td>9 WKS PTA</td>
<td>Start training program at home until 13 wks PTA</td>
</tr>
<tr>
<td>12 WKS PTA</td>
<td>Prechtl's General Movements Assessment (GMs)</td>
</tr>
<tr>
<td></td>
<td>Imitation Assessment (IA)</td>
</tr>
<tr>
<td>14 WKS PTA</td>
<td>Prechtl's General Movements Assessment (GMs) Assessment of Reaching and Grasping (RG)</td>
</tr>
<tr>
<td></td>
<td>Infant Hand Assessment (IHA)</td>
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<tr>
<td>16 WKS PTA</td>
<td>Prechtl's General Movements Assessment (GMs) Assessment of Reaching and Grasping (RG)</td>
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<td>Infant Hand Assessment (IHA)</td>
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<tr>
<td>18 WKS PTA</td>
<td>Prechtl's General Movements Assessment (GMs) Assessment of Reaching and Grasping (RG)</td>
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<td>Infant Hand Assessment (IHA)</td>
</tr>
<tr>
<td>6 MTHS PTA</td>
<td>Bayley Scales of Infant and Toddler Development (Bayley III)</td>
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<tr>
<td></td>
<td>Electroencephalogram (EEG)</td>
</tr>
<tr>
<td>12 MTHS PTA</td>
<td>Bayley Scales of Infant and Toddler Development (Bayley III)</td>
</tr>
</tbody>
</table>
REFERRAL TO UP-BEAT STUDY

Name of referrer: ____________________________________________________________
Organisation: ________________________________________________________________
Profession: ________________________________________________________________
Address: Phone Number: ______________________________________________________
Fax Number: Email Address: ______________________________________________________
Name of referrer: ____________________________________________________________
Organisation: ________________________________________________________________
Profession: ________________________________________________________________
Address: Phone Number: ______________________________________________________
Fax Number: Email Address: ______________________________________________________

Hospital Record Number: ______________________________________________________

1. This referral has been verified by the child’s treating Paediatrician? Yes / No
   Name of treating Paediatrician: ___________________________________________
   Address: Phone Number: ___________________________________________________

2. The parent of the child has given permission for their contact details to be passed on to the
   investigators of the UP-BEAT study. Yes / No

3. The study flyer with investigator’s contact number has been passed onto the parent of the child.
   Yes / No

Please note that the parent must be aware of this referral under privacy guidelines, for information to be given
   to us. The study flyer can also be provided to parents to enable self referral to the study.

Signed: ___________________________ Date: ___________________________
Send to:

UP-BEAT PhD Student
Attention: Micah Perez
Queensland Cerebral Palsy & Rehabilitation Research Centre UQ
Dept of Paediatrics & Child Health,
Level 7, Block 6, Royal Brisbane & Women’s Hospital HERSTON
QLD 4029

Phone: 0418 122 544 or 3646 5372 Email: m.perez1@uq.edu.au

OR

UP-BEAT Chief Investigator
Attention: Prof. Roslyn Boyd
Queensland Cerebral Palsy & Rehabilitation Research Centre UQ
Dept of Paediatrics & Child Health,
Level 7, Block 6, Royal Brisbane & Women’s Hospital HERSTON
QLD 4029

Phone: 0423 076 739 or 3365 5315 Email: r.boyd@uq.edu.au
9.13. Study documents – Study parent general information forms
STANDARD PARENT/GUARDIAN INFORMATION STATEMENT – BRAIN INJURY COHORT
(page 1 of 6)


INVESTIGATORS: Dr Andrea Guzzetta, Prof Roslyn Boyd, Prof Virginia Slaughter, Prof Paul Colditz, Ms Imogen Fisher, , Prof Thomas Suddendorf, Dr Mark Nielsen, Ms Janine Oostenbroek, Mrs Lisa Findlay, Dr Lynne McKinlay, Dr Kate Sinclair, A/Prof Stephen Rose, Dr Koa Whittingham, Prof Jenny Ziviani, Ms Micah Perez, Mrs Christine Finn and Mrs Bernadette Shannon.

Thank you for taking the time to read this Information Statement.
This information statement and consent is 6 pages long. Please make sure you have all the pages.

For people who speak languages other than English:
If you would also like information about the research and the Consent Form in your language, please ask the person explaining this project to you.

Your child is invited to participate in a Research Project that is explained below.

What is an Information Statement?
These pages contain information about a research project we are inviting your child to take part in. The purpose of this information is to explain to you clearly and openly all the steps and procedures of this project. The information is to help you to decide whether or not you would like your child to take part in the research.

Please read this information carefully. You can ask us questions about anything in it. You may also wish to talk about the project with others eg friends or health care worker. Once you have understood what the project is about, if you would like your child to take part please sign the consent form at the end of this information statement. You will be given a copy of this information and consent form to keep.

WHAT IS THE RESEARCH PROJECT ABOUT?
This project is about infants with asymmetrical brain injury (only one side of the brain is impaired or one side is significantly more impaired than the other) that occurred during pregnancy or around birth. These infants can show an impaired development of motor function that, when present, primarily involves the hand function of the limb opposite to the side of the injury (or the side of the brain that is more impaired). To reduce impairment of hand function, early treatments are generally performed involving the promotion of goal-directed hand actions, such as reaching for a toy or manipulating it. However, these treatments are not fully feasible before the age of 4 or 5 months, as goal-directed movements are not sufficiently mature.

This project will explore the effects of interventions performed before the age of 3 months. Two types of intervention will be compared in our study. The first one is called Action Observation Training. It consists of daily sessions in which one of the parents of the baby shows him/her some
hand actions (grasping) performed on a toy. The second one is called Toy Observation Training. It consists of daily sessions in which one of the parents of the baby shows him/her a toy. The Action Observation Training will encourage the baby to focus on the action of the hand. This can promote the development of appropriate hand actions by imitation. The Toy Observation Training will encourage the baby to focus on the characteristics of the object. This can promote the development of appropriate hand actions by selection of the movements based on the characteristics of the toy. As part of the same project, a cohort of 40 healthy term infants will be assessed with the same protocol.

WHO ARE THE RESEARCHERS?
All the researchers work at the Royal Children’s Hospital (Brisbane), the Royal Brisbane Women’s Hospital or the University of Queensland.
1. Dr Andrea Guzzetta is a Paediatric Neurologist and senior researcher. He has defined the protocol and will coordinate the project.
2. Professor Roslyn Boyd is a Paediatric Physiotherapist. She will coordinate the project and supervise the assessments and home programs.
3. Professor Virginia Slaughter and Professor Thomas Suddendorf, Dr Mark Nielsen and Ms Janine Oostenbroek are Psychologists and will coordinate the study on the normal development of hand functions in relation to the training.
4. Professor Paul Colditz is a medical doctor and will be involved in particular with the infant assessment of general movements and with the EEG.
5. Bernadette Shannon, Lisa Findlay and Imogen Fisher are Occupational Therapists conducting research. They will do assessments and help to run the treatment programs.
6. Christine Finn is a Physiotherapist conducting research. She will assist with assessments.
7. Dr Lynne McKinlay and Dr Kate Sinclair are Paediatricians and will coordinate and supervise clinical follow-up of the infants with asymmetrical brain damage.
8. Dr Koa Whittingham is a Psychologist and will be involved with the assessment of developmental outcomes of infants with a symmetric brain injury.
9. Professor Stephen Rose is a Physicist and Group Leader in Imaging Research at the University of Queensland Centre for Clinical Research (UQCCR) and will contribute to the analysis of clinical imaging, with Dr Andrea Guzzetta and Dr Sinclair, mainly with the cohort of infants with asymmetrical brain damage.
10. Prof Jenny Ziviani is a Paediatric Occupational Therapist. She will oversee and supervise the project, and provide co-supervision with A/Prof Roslyn Boyd for the PhD student.
11. Micah Perez is an Occupational Therapist and PhD Student conducting research. She will coordinate the selection and recruitment process of the cohort of infants with asymmetrical brain damage, and help with assessments and the treatment programs.

WHY IS MY CHILD BEING ASKED TO BE IN THIS RESEARCH PROJECT?
You have been invited to participate because your baby is younger than 9 weeks and was diagnosed with an asymmetrical brain injury on ultrasound or MRI. This study will be looking at the benefits that this early intervention may have for your baby. You live within 200 km radius of the Royal Children’s Hospital and could be visited at home.
organized, to allow supervision of the training activities and for assessments. Follow-up questions on how to perform the training activities will be addressed by telephone or during testing visits. Parents will be asked to video-record the sessions each day, so that changes in babies response to the training can be tracked. All the babies who participate will take part in a number of assessments. The following assessments will be performed at the infant’s home by a researcher.

1. **Assessment of reaching and grasping**
   This is the primary outcome measure of the study, which will be performed at 14, 16 and 18 weeks. The assessment will last about 15 minutes and will be performed at home. The baby will be secured in a custom-made infant chair with a large chest strap, allowing full range of motion of the arms. The assessment consists of the video-recording of the interaction between the baby and different toys presented sequentially. Some of the toys will contain a pressure sensor that will enable us to measure the force of the baby’s hands during grasping. Other measures will be the number of reaches and their duration. All the measures will be obtained either from the video-recording or from the computer storing the information about pressure.

2. **Assessment of hand function**
   This assessment will be performed at 14, 16 and 18 weeks and at 6 months. It will last about 15 minutes. The test consists of 20 different items that score the responses of the baby to the presentation of a series of toys in different conditions (on the midline, from the side, bilaterally etc.). The final score represents a global estimate of infant hand motor development. The assessment will be video-recorded.

3. **Assessment of spontaneous movements**
   This assessment will be performed at 9, 12, 14, 16 and 18 weeks. It will last about 10 minutes. It consists of the analysis of the quality of spontaneous motility from a short video-recording. Video-recordings will last from 5 to 10 minutes. The video-camera will be positioned in the midline approximately one meter above the infant, at an angle of 45°. Infants will be recorded during wakefulness at inter-feeding time, in supine position, naked or in a nappy. The analysis of the GMs will be performed by one of the certified GMs assessors participating to the study, blinded of the infants’ group.

4. **Assessment of imitation**
   This assessment will be performed at 9 and 12 weeks. It will last about 5 minutes. Infants will be presented with some simple gestures and their reactions will be video-recorded. Common gestures will be used, such as facial gestures, manual gestures, and vocal gestures. The quality of imitation will be assessed from the video-recordings.

Only the following 2 assessments will be performed at the Royal Children’s Hospital at 6 and at 12 months.

5. **Developmental Scale**
   This assessment will be performed at 6 and 12 months. A standardised developmental scale called Bayley III will be used to assess cognitive development, language and motor abilities. It will consist of a series of simple interactions with the infants and will take between 50 and 80 minutes to administer.
6. EEG

This test will be performed at 6 months post-term and will last about 25 minutes. EEG is a standard method in babies to measure brain waves and record them to a computer. We will use a certified advanced system extensively used in infant testing, called geodesic Sensor Net. It involves applying a smooth net of electrodes on the head, as a swimming cap. It is applied in few seconds and most infants forget they are wearing the net soon after it is applied.

The timing of the assessments is summarized in the following table.

<table>
<thead>
<tr>
<th>Assessment of reaching &amp; grasping</th>
<th>6ws</th>
<th>9ws</th>
<th>12ws</th>
<th>14ws</th>
<th>16ws</th>
<th>18ws</th>
<th>6ms</th>
<th>12ms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assessment of hand function</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Assessment of spontaneous movements</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
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<tr>
<td>Assessment of imitation</td>
<td>●</td>
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<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Developmental scale (Bayley III)</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
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<tr>
<td>EEG</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Approximate duration of the assessment</td>
<td>15min</td>
<td>15min</td>
<td>25min</td>
<td>25min</td>
<td>25min</td>
<td>100min</td>
<td>65min</td>
<td></td>
</tr>
</tbody>
</table>

**IS THERE LIKELY TO BE A BENEFIT TO MY CHILD?**
Your child will receive 4 weeks of a new intervention. Regardless of the group your child is in, you are likely to see improvements in your child’s arm and hand skills. You will also receive a summary report at the conclusion of the study containing the results in plain language of all the assessments performed.

**IS THERE LIKELY TO BE A BENEFIT TO OTHER PEOPLE IN THE FUTURE?**
We hope that the results of our project will help other children with asymmetric brain injury and their families in the future. If we find that this new form of very early treatment has a better and longer lasting effect on hand and arm skills it may change the way we provide treatment in the future. Better outcomes for upper limb rehabilitation, may improve children’s ability to participate in a range of new activities, and reduce the burden of care on families/caregivers.

**WHAT ARE THE POSSIBLE RISKS AND/OR SIDE EFFECTS?**
We do not expect that there will be any risks or side effects from receiving either treatment, as they are totally non-invasive and based on simple observations of actions followed by toy manipulation. The EEG is a completely safe clinical procedure that is commonly used in newborns and infants. In addition, for this project we will use a new advanced tool called Geodesic Sensor Net, which is currently the most baby-friendly among the products available.
WHAT ARE THE POSSIBLE DISCOMFORTS AND/OR INCONVENIENCES?
The entire training will be performed at home by one of the parents or caregivers. They will involve only 15 minutes intervention per day, in a play setting performed in three 5 minute sessions. All the assessment appointments, except the last two at 6 and 12 months, will be performed at home and will be planned to minimize any inconvenience to you.

WHAT WILL BE DONE TO MAKE SURE THE INFORMATION IS CONFIDENTIAL?
All results of assessments will be stored without your child’s name on them. A number will be used to identify them. This number will be linked to your child’s name but the linking file will be kept confidential and only made available to the researchers. Data collection sheets recording the assessment scores and the videotapes of the assessments and group program will be stored in a secure filing cabinet and only the researchers will have access to this information. On the video tapes your child will be able to be identified and these tapes will be used for assessment purposes only for this study. These video tapes would not be used for teaching or promotional material for the project without directly seeking your permission separate to your child participating in this study. These data sheets and videos will be kept at the RCH in a locked filing cabinet until your child is 25 years old, and then destroyed. If we give talks or write about the results of this project, we will not use any names or identifying details.

WILL I BE INFORMED OF THE RESULTS WHEN THE RESEARCH PROJECT IS FINISHED?
If at any time you would like information about your child’s results, an appointment will be organized with one of the researchers. A 6 monthly newsletter will also be sent to you about the progress of the study. At the end of the study, all families will be sent a summary of the results. The newsletter and final summary will talk about the children as a group and your child will not be identified in person.

You can decide whether or not to give permission for your child to take part in this research project. You can decide whether or not you would like to withdraw your child at any time without explanation.

You may like to discuss your child’s participation in this research project with your family and with your doctor. You can ask for further information before deciding to take part. If you would like more information about the study or if you need to contact a study representative in an emergency, the person to contact is:

Name: Professor Roslyn Boyd
Contact telephone: 0434 608 443
WHAT ARE MY CHILD'S RIGHTS AS A PARTICIPANT?

- I am informed that except where stated above, no information regarding my child's medical history will be released. This is subject to legal requirements.
- I am informed that the results of any tests involving my child will not be published so as to reveal my child's identity. This is subject to legal requirements.
- The detail of the procedure proposed has also been explained to me. This includes how long it will take, how often the procedure will be performed and whether any discomfort will result.
- It has also been explained that my child's involvement in the research may not be of any benefit to him or her. I understand that the purpose of this research project is to improve the quality of medical care in the future.
- I have been asked if I would like to have a family member or a friend with me while the project is explained to me.
- I understand that this project follows the guidelines of the National Statement on Ethical Conduct in Research Involving Humans (1999).
- I understand that this research project has been approved by the Royal Children’s Hospital Ethics in Human Research Committee on behalf of the Royal Children’s Hospital Board.
- I have received a copy of this document.

ETHICS CONTACT:
The Human Research Ethics Committee of the Royal Children’s Hospital and Health Services District has approved this study. Should you wish to discuss the study with someone not directly involved, in particular in relation to matters concerning policies, information about the conduct of the study or your rights as a participant, or if you wish to make a confidential complaint, please contact:

RCH&HSD Ethics Committee Coordinator
Royal Children’s Hospital and Health Services District
C/- Dept of Pediatrics and Child Health
Level 3, RCH Foundation Building
Royal Children’s Hospital
Herston Road
Herston QLD 4029
Tel: (07) 3646 9167 (Monday to Friday 9am-5pm)
STANDARD PARENT/GUARDIAN INFORMATION STATEMENT – HEALTHY COHORT


INVESTIGATORS: Dr Andrea Guzzetta, Prof Roslyn Boyd, Prof Virginia Slaughter, Prof Paul Colditz, Ms Imogen Fisher, Prof Thomas Suddendorf, Dr Mark Nielsen, Ms Janine Oostenbroek, Mrs Lisa Findlay, Dr Lynne McKinlay, Dr Kate Sinclair, A/Prof Stephen Rose, Dr Koa Whittingham, Prof Jenny Ziviani, Ms Micah Perez, Mrs Christine Finn and Mrs Bernadette Shannon.

Thank you for taking the time to read this Information Statement.

This information statement and consent is 6 pages long. Please make sure you have all the pages.

For people who speak languages other than English:
If you would also like information about the research and the Consent Form in your language, please ask the person explaining this project to you.

Your child is invited to participate in a Research Project that is explained below.

What is an Information Statement?
These pages contain information about a research project we are inviting your child to take part in. The purpose of this information is to explain to you clearly and openly all the steps and procedures of this project. The information is to help you to decide whether or not you would like your child to take part in the research.

Please read this information carefully. You can ask us questions about anything in it. You may also wish to talk about the project with others eg friends or health care worker. Once you have understood what the project is about, if you would like your child to take part please sign the consent form at the end of this information statement. You will be given a copy of this information and consent form to keep.

WHAT IS THE RESEARCH PROJECT ABOUT?
In the present project we want to explore whether with a simple training performed before 3 months of life we can influence the development of hand function in healthy term infants. This is important because then we will be able to apply the same training in infants with early brain injury, thus trying to improve their motor outcome.

Two types of training will be compared in the study. The first one is called Action Observation Training. It consists of daily sessions in which one of the parents of the baby shows him/her some hand actions (grasping) performed on a toy, and then gives the toy to the baby to manipulate. The second one is called Toy Observation Training. It consists of daily sessions in which one of the parents of the baby shows him/her a toy. The Action Observation Training will encourage the baby...
to focus on the action of the hand. This can promote the development of appropriate hand actions by imitation.

The Toy Observation Training will encourage the baby to focus on the characteristics of the object. This can promote the development of appropriate hand actions by selection of the movements based on the characteristics of the toy.

As part of the same project, a cohort of 32 infants with asymmetrical brain injury will be also recruited and assessed with the same protocol.

WHO ARE THE RESEARCHERS?

All the researchers work at the Royal Children’s Hospital (Brisbane), the Royal Brisbane Women’s Hospital or University of Queensland.

1. Dr Andrea Guzzetta is a Paediatric Neurologist and senior researcher. He has defined the protocol and will coordinate the project.
2. Professor Roslyn Boyd is a Paediatric Physiotherapist. She will coordinate the project and supervise the assessments and group treatments.
3. Professor Virginia Slaughter and Professor Thomas Suddendorf, Dr Mark Nielsen and Ms Janine Oostenbroek are Psychologists and will coordinate the study on the normal development of hand functions in relation to the training.
4. Professor Paul Colditz is a medical doctor and will be involved in particular with the infant assessment of general movements and with the EEG.
5. Bernadette Shannon, Lisa Findlay and Imogen Fisher are Occupational Therapists conducting research. They will do assessments and help to run the treatment programs.
6. Christine Finn is a Physiotherapist conducting research. She will assist with assessments.
7. Dr Lynne McKinlay and Dr Kate Sinclair are Paediatricians and will coordinate and supervise clinical follow-up of the infants with asymmetrical brain damage.
8. Dr Koa Whittingham is a Psychologist and will be involved with the assessment of developmental outcomes of infants with asymmetric brain injury.
9. Professor Stephen Rose is a Physicist and Group Leader in Imaging Research at the University of Queensland Centre for Clinical Research (UQCCR) and will contribute to the analysis of clinical imaging, with Dr Andrea Guzzetta and Dr Sinclair, mainly with the cohort of infants with asymmetrical brain damage.
10. Prof Jenny Ziviani is a Paediatric Occupational Therapist. She will oversee and supervise the project, and provide co-supervision with Prof Roslyn Boyd for the PhD student.
11. Micah Perez is an Occupational Therapist and PhD Student conducting research. She will coordinate the selection and recruitment process of the cohort of infants with asymmetrical brain damage, and help with assessments and the treatment programs.

WHY IS MY CHILD BEING ASKED TO BE IN THIS RESEARCH PROJECT?

You have been invited to participate because your baby is a healthy term infant. This study will be looking at the effects that this early training may have for your baby, in order to contribute to the establishment of new treatments for infants with early brain injury.
WHAT ARE MY CHILD’S ALTERNATIVES TO PARTICIPATING IN THIS PROJECT?
There is no obligation to participate in this project.

WHAT DOES MY CHILD NEED TO DO TO BE IN THIS RESEARCH PROJECT?
Babies and parents taking part to the study will be randomly assigned to one of two intervention groups (as by the flip of a coin, completely by chance). The intervention will be performed by one of the parents and will have a duration of 4 weeks, from baby’s 9th to 13th week of age. Sundays will be excluded. Three daily sessions of 5 minutes each will be performed each day. Parents will receive training by an occupational therapist directly at home for approximately 30 minutes. During the 4 weeks of training home visits by the occupational therapist will also be organized, to allow supervision of the training activities and for assessments. Follow-up questions on how to perform the training activities will be addressed by telephone or during testing visits. Parents will be asked to video-record the sessions each day so that changes in baby’s response to the training can be tracked.

All the babies who participate will take part in a number of assessments. The following assessments will be performed at the infant’s home by a researcher.

1. Assessment of reaching and grasping
This is the primary outcome measure of the study, which will be performed at 14, 16 and 18 weeks. The assessment will last about 15 minutes.
The baby will be secured in a custom-made infant chair with a large chest strap, allowing full range of motion of the arms. The assessment consists of the video-recording of the interaction between the baby and different toys presented sequentially. Some of the toys will contain a pressure sensor that will enable us to measure the force of the baby’s hands during grasping. Other measures will be the number of reaches and their duration. All the measures will be obtained either from the video-recording or from the computer storing the information about pressure.

2. Assessment of hand function
This assessment will be performed at 14, 16 and 18 weeks and also at 6 months. It will last about 15 minutes.
The test consists of 20 different items that score the responses of the baby to the presentation of a series of toys in different conditions (on the midline, from the side, bilaterally etc.). The final score represents a global estimate of infant hand motor development. The assessment will be video-recorded.

3. Assessment of spontaneous movements (General movements)
This assessment will be performed at 9, 12, 14, 16 and 18 weeks. It will last about 10 minutes.
It consists of the analysis of the quality of spontaneous motility from a short video-recording. Video-recordings will last from 5 to 10 minutes. The video-camera will be positioned in the midline approximately one meter above the infant, at an angle of 45°. Infants will be recorded during wakefulness at inter-feeding time, in supine position, naked or in a nappy. The analysis of the GMs will be performed by one of the certified GMs assessors participating to the study, blinded of the infants’ group.

4. Assessment of imitation
This assessment will be performed at 9 and 12 weeks. It will last about 5 minutes.
Infants will be presented with some simple gestures and their reactions will be video-recorded. Common gestures will be used, such as facial gestures, manual gestures, and vocal gestures. The quality of imitation will be assessed from the video-recordings.

Only the following 2 assessments will be performed at the Royal Children’s Hospital at 6 and 12 months.

5. Developmental Scale
This assessment will be performed at 6 and 12 months. A standardised developmental scale called Bayley III will be used to assess cognitive development, language and motor abilities. It will consist of a series of simple interactions with the infants and will take between 50 and 80 minutes to administer.

6. EEG
This test will be performed at 6 months post-term and will last about 25 minutes. EEG is a standard method in babies to measure brain waves and record them to a computer. We will use a certified advanced system extensively used in infant testing, called geodesic Sensor Net. It involves applying a smooth net of electrodes on the head, as a swimming cap. It is applied in few seconds and most infants forget they are wearing the net soon after it is applied.

The timing of the assessments is summarized in the following table.

<table>
<thead>
<tr>
<th>Assessments at home</th>
<th>Assessments at RCH/UQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assessment of reaching &amp; grasping</td>
<td>● ● ●</td>
</tr>
<tr>
<td>Assessment of hand function</td>
<td>● ● ● ●</td>
</tr>
<tr>
<td>Assessment of spontaneous movements</td>
<td>● ● ● ●</td>
</tr>
<tr>
<td>Assessment of imitation</td>
<td>● ●</td>
</tr>
<tr>
<td>Developmental scale (Bayley III)</td>
<td>● ●</td>
</tr>
<tr>
<td>EEG</td>
<td>●</td>
</tr>
<tr>
<td>Approximate duration of the assessment</td>
<td>15min 15min 25min 25min 25min 100min 65min</td>
</tr>
</tbody>
</table>

**IS THERE LIKELY TO BE A BENEFIT TO MY CHILD?**
Your child will receive 4 weeks of a training that may determine mild improvements in your child’s grasping and reaching skills. You will also receive a summary report at the conclusion of the study containing the results in plain language of all the assessments performed.

**IS THERE LIKELY TO BE A BENEFIT TO OTHER PEOPLE IN THE FUTURE?**
We hope that the results of our project will help infants with asymmetric brain injury and their families in the future. If we find that this new form of very early training has some effects on hand and arm skills, it may change the way we provide treatment in the future. Better outcomes for upper limb rehabilitation, may improve children’s ability to participate in a range of new activities, and reduce the burden of care on families/caregivers.
WHAT ARE THE POSSIBLE RISKS AND/OR SIDE EFFECTS?
We do not expect that there will be any risks or side effects from receiving either treatment, as they are totally non-invasive and based on simple observations of actions followed by toy manipulation. The EEG is a completely safe clinical procedure that is commonly used in newborns and infants. In addition, for this project we will use a new advanced tool called Geodesic Sensor Net, which is currently the most baby-friendly among the products available.

WHAT ARE THE POSSIBLE DISCOMFORTS AND/OR INCONVENIENCES?
The entire training will be performed at home by one of the parents or caregivers. It will involve only 15 minutes intervention per day, in a play setting in three 5 minute sessions. All the assessment appointments, except the last two at 6 and 12 months, will be performed at home and will be planned to minimize any inconvenience to you.

WHAT WILL BE DONE TO MAKE SURE THE INFORMATION IS CONFIDENTIAL?
All results of assessments will be stored without your child’s name on them. A number will be used to identify them. This number will be linked to your child’s name but the linking file will be kept confidential and only made available to the researchers. Data collection sheets recording the assessment scores and the videotapes of the assessments and group program will be stored in a secure filing cabinet and only the researchers will have access to this information. On the video tapes your child will be able to be identified and these tapes will be used for assessment purposes only for this study. These video tapes would not be used for teaching or promotional material for the project without directly seeking your permission separate to your child participating in this study. These data sheets and videos will be kept at the RCH in a locked filing cabinet until your child is 25 years old, and then destroyed. If we give talks or write about the results of this project, we will not use any names or identifying details.

WILL I BE INFORMED OF THE RESULTS WHEN THE RESEARCH PROJECT IS FINISHED?
If at any time you would like information about your child’s results, an appointment will be organized with one of the researchers. A 6 monthly newsletter will also be sent to you about the progress of the study. At the end of the study, all families will be sent a summary of the results. The newsletter and final summary will talk about the children as a group and your child will not be identified in person. You can decide whether or not to give permission for your child to take part in this research project. You can decide whether or not you would like to withdraw your child at any time without explanation.

You may like to discuss your child's participation in this research project with your family and with your doctor. You can ask for further information before deciding to take part. If you would like more information about the study or if you need to contact a study representative in an emergency, the person to contact is:

Name: Professor Roslyn Boyd
Contact telephone: 0434 608 443

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WHAT ARE MY CHILD’S RIGHTS AS A PARTICIPANT?

- I am informed that except where stated above, no information regarding my child’s medical history will be released. This is subject to legal requirements.
- I am informed that the results of any tests involving my child will not be published so as to reveal my child’s identity. This is subject to legal requirements.
- The detail of the procedure proposed has also been explained to me. This includes how long it will take, how often the procedure will be performed and whether any discomfort will result.
- It has also been explained that my child’s involvement in the research may not be of any benefit to him or her. I understand that the purpose of this research project is to improve the quality of medical care in the future.
- I have been asked if I would like to have a family member or a friend with me while the project is explained to me.
- I understand that this project follows the guidelines of the National Statement on Ethical Conduct in Research Involving Humans (1999).
- I understand that this research project has been approved by the Royal Children’s Hospital Ethics in Human Research Committee on behalf of the Royal Children’s Hospital Board.
- I have received a copy of this document.

ETHICS CONTACT:
The Human Research Ethics Committee of the Royal Children’s Hospital and Health Services District has approved this study. Should you wish to discuss the study with someone not directly involved, in particular in relation to matters concerning policies, information about the conduct of the study or your rights as a participant, or if you wish to make a confidential complaint, please contact:

RCH&HSD Ethics Committee Coordinator
Royal Children’s Hospital and Health Services District
C/- Dept of Pediatrics and Child Health
Level 3, RCH Foundation Building
Royal Children’s Hospital
Herston Road
Herston QLD 4029
Tel: (07) 3646 9167 (Monday to Friday 9am-5pm)
STANDARD INFORMED CONSENT FOR PARENT/GUARDIAN TO GIVE CONSENT FOR THEIR CHILD TO PARTICIPATE IN A RESEARCH PROJECT

Project Number

Title of Project
The effect of infant action observation training on the early development of hand reaching and grasping in healthy infants and in infants with early brain injury.

Investigator(s)
Dr Andrea Guzzetta, Prof Roslyn Boyd, Prof Virginia Slaughter, Prof Paul Colditz, Ms Imogen Fisher, Prof Thomas Suddendorf, Dr Mark Nielsen, Ms Janine Oostenbroek, Mrs Lisa Findlay, Dr Lynne McKinlay, Dr Kate Sinclair, A/Prof Stephen Rose, Dr Koa Whittingham, Prof Jenny Ziviani, Ms Micah Perez, Mrs Christine Finn and Mrs Bernadette Shannon.

I (Parent/Guardian name) voluntarily consent for my child to take part in the above titled Research Project, explained to me by Mr/Ms/Dr/Professor

- I have received a Parent/Guardian Information Statement to keep and I believe I understand the purpose, extent and possible effects of my child's involvement
- I have been asked if I would like to have a family member or friend with me while the project was explained
- I have had an opportunity to ask questions and I am satisfied with the answers I have received
- I understand that the researcher has agreed not to reveal results of any information involving my child, subject to legal requirements
- If information about this project is published or presented in any public form, I understand that the researcher will not reveal my child's identity
- I understand that if I refuse to consent to my child's participation, or if I withdraw my child from the project at any time without explanation, this will not affect my child's access to the best available treatment options and care from the Royal Children's Hospital
- I understand I will receive a copy of this consent form

- I consent for my child to participate in this research project

YES □ NO □

SIGNATURE ____________________________ Date ____________

I have explained the study to the parent/guardian who has signed above, and believe that they understand the purpose, extent and possible effects of their child's involvement in this study.

RESEARCHER'S SIGNATURE ____________________________ Date ____________

Note: All parties signing the Consent Form must date their own signature.
9.15. Study documents – Study video consent form
UP-BEAT STUDY

Video and Photographic Consent

I, ___________________________________________(print full name) give consent for photos and/or video images to be taken of my son/daughter as part of this study to be used for:-

☐ Education presentations/posters

☐ Promotional information/flyers

☐ Queensland Cerebral Palsy and Rehabilitation Research Centre Website

If at any time in the future you wish to withdraw your consent please phone or email the Queensland Cerebral Palsy and Rehabilitation Research Centre.

Name of child _____________________________________________________

Legal Guardian _____________________________________________________

Relationship to Child _________________________________________________

Signature (Legal Guardian)____________________________ Date____________
9.16. Study documents – Parent contact and general information form
UP-BEAT STUDY: Parent and Baby Information Sheet

BABY’S NAME: ________________________________________________________________________
DOB: ________________________ GENDER: male / female
GESTATION AT BIRTH: ______________________________________________________________
PLACE OF BIRTH: _________________________________________________________________
HOSPITAL RECORD No. (If applicable): _______________________________________________
SIBLINGS & DOB: __________________________________________________________________

PARENTS NAMES: _____________________________________________________________________
ADDRESS: _________________________________________________________________________
PHONE NO: ________________________ MOBILE: ________________________ E-MAIL ADDRESS:

PREFERRED CONTACT METHOD & TIME: _________________________________________________

PREGNANCY / BIRTH HISTORY / HEALTH HISTORY: ___________________________________
___________________________________________________________________________________
___________________________________________________________________________________
___________________________________________________________________________________

CULTURAL BACKGROUND: __________________________________________________________
PARENT EDUCATION LEVEL: _________________________________________________________
CURRENT EMPLOYMENT: _____________________________________________________________

ADDITIONAL CONTACT (eg grandparents)
NAMES: _________________________________________________________________________
ADDRESS: ________________________________________________________________________
PHONE NO: ________________________ MOBILE: ________________________ E-MAIL ADDRESS:

Micah Perez - Thesis Appendices
9.17. Study documents – Study schedule form
UP-BEAT STUDY - ASSESSMENT AND INTERVENTION SCHEDULE

< 9 weeks post-term age: RECRUITMENT – information and consent forms signed
– general information form completed

9 weeks post-term age (+/- 3 days): ASSESSMENT – home visit to video General Movements Assessment and Imitation Assessment

INTERVENTION – parent training and commencement

9-13 weeks post-term age: INTERVENTION – 3 times / day by parent

12 weeks post-term age: ASSESSMENT – home visit to video General Movements Assessment and Imitation Assessment

14 weeks post-term age: ASSESSMENT – home visit to video General Movements Assessment, Reaching & Grasping Assessment and Infant Hand Assessment

16 weeks post-term age: ASSESSMENT – home visit to video General Movements Assessment, Reaching & Grasping Assessment and Infant Hand Assessment

18 weeks post-term age: ASSESSMENT – home visit to video General Movements Assessment, Reaching & Grasping Assessment and Infant Hand Assessment

6 months post-term age: ASSESSMENT at RCH – Infant Hand Assessment, Bayley III Developmental Assessment and EEG

12 months post-term age: ASSESSMENT at RCH – Bayley III Developmental Assessment
9.18. Study documents – Action Observation
Training sheet for parents
**Routine:**
- 3 sessions per day: each session is 5 minutes
- 6 days a week with one day off (your choice)
- 4 weeks (9-13 weeks: +/- 3 days)

**Equipment:**
- video camera and tripod positioned so that you and baby are visible
- 3 toys
- stopwatch
- video record sheet and pen

**The training:**
1. Turn on the camera and hold the sheet (with day and session marked) up to the camera. Then start the stopwatch.

2. Hold your right hand (use left for next training session) in front of baby’s face at just more than their arm’s length. Bring the toy with your left hand (right for next session) to your right hand and grasp the toy by slowly wrapping your fingers around it and taking it from the left hand.

   If baby is not attending, wiggle your fingers of your grasping hand to gain baby’s attention so they are looking at your hand and the toy. Repeat this grasp action for five minutes in total. If the baby is not attending or if there are distractions that interrupt the training, allow the baby to play briefly with the toy by placing it their hand (alternate which of the baby’s hands you put the toy into) stop the clock then restart when the training continues. Alternate the 3 toys as needed to keep the baby’s attention.

   If you need to change hands during one session, please change hands out of baby’s view.

3. If baby is not attending, wiggle your fingers of your grasping hand to gain baby’s attention so they are looking at your hand and the toy. Repeat this grasp action for five minutes in total. If the baby is not attending or if there are distractions that interrupt the training, allow the baby to play briefly with the toy by placing it their hand (alternate which of the baby’s hands you put the toy into) stop the clock then restart when the training continues. Alternate the 3 toys as needed to keep the baby’s attention.

4. Turn off camera.
5. Can you please make a record in the diary provided?
9.19. Study documents – Toy Observation
Training sheet for parents
Toy Observation Training

Routine:
- 3 sessions per day: each session is 5 minutes
- 6 days a week with one day off (your choice)
- 4 weeks (9-13 weeks: +/- 3 days)

Equipment:
- video camera and tripod positioned so that you and baby are visible
- 3 toys
- stopwatch
- video record sheet and pen

The training:
1. Turn on the camera and hold the sheet (with day and session marked) up to the camera.

2. Start the stop watch

3. Hold the toy in front of your baby’s face at just more than their arm’s length.
   Wiggle the toy or move the toy slowly to maintain baby’s attention so they are looking at the toy. Continue for five minutes in total, alternating the toys if necessary to keep baby’s attention.
   If your baby is not attending or if there are distractions that interrupt the training, stop the clock and allow the baby to play briefly with the toy by placing it their hand (alternate which of the baby’s hands you put the toy into) then restart the clock when the training continues. If you need to change hands during one session, please change hands out of baby’s view.

4. Turn off camera.
5. Can you please make a record in the diary provided?
9.20. Study documents – Parent Diary template
Parent Diary & Comments

Please tick if you did the training session and add any comments or problems.

<table>
<thead>
<tr>
<th>WEEK 1</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thurs 25th October</td>
<td>□ 2 □ 3</td>
</tr>
<tr>
<td>Fri 26th October</td>
<td>□ 2 □ 3</td>
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<tr>
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<td>□ 2 □ 3</td>
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<tr>
<td>Sun 28th October</td>
<td>□ 2 □ 3</td>
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<tr>
<td>Mon 29th October</td>
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<tr>
<td>Tues 30th October</td>
<td>□ 2 □ 3</td>
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<tr>
<td>Weds 31st October</td>
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<table>
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</tr>
<tr>
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<td>□ 2 □ 3</td>
</tr>
<tr>
<td>Sat 3rd November</td>
<td>□ 2 □ 3</td>
</tr>
<tr>
<td>Sun 4th November</td>
<td>□ 2 □ 3</td>
</tr>
<tr>
<td>Mon 5th November</td>
<td>□ 2 □ 3</td>
</tr>
<tr>
<td>Tues 6th November</td>
<td>□ 2 □ 3</td>
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<tr>
<td>Weds 7th November</td>
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<table>
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<td>Sat 10th November</td>
<td>□ 2 □ 3</td>
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<tr>
<td>Sun 11th November</td>
<td>□ 2 □ 3</td>
</tr>
<tr>
<td>Mon 12th November</td>
<td>□ 2 □ 3</td>
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<tr>
<td>Tues 13th November</td>
<td>□ 2 □ 3</td>
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<tr>
<td>Weds 14th November</td>
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<table>
<thead>
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<tr>
<td>Fri 16th November</td>
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<td>Sat 17th November</td>
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<tr>
<td>Sun 18th November</td>
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<td>Mon 19th November</td>
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<td>Tues 20th November</td>
<td>□ 2 □ 3</td>
</tr>
<tr>
<td>Weds 21st November</td>
<td>□ 2 □ 3</td>
</tr>
</tbody>
</table>

If you have any questions or concerns about your appointments or the study in general please call Bernadette Shannon on 3646 5060

If you have any questions or concerns about the training please call Micah Perez on 3646 5372 or 0418 122 544

Or Lisa Findlay 0400 337 993
9.21. Study documents – Medical History Checklist at study enrolment
### Aetiology

**Known cause and location of brain lesion**

| Trauma, arterial stroke, venous infarction, IVH, PVL, encephalitis, cerebral malformation |

**Exclude:**
- seizures uncontrolled with medication
- hydrocephalus
- grade III or IV ROP

**Timing of event**

| Pre-natal (1\textsuperscript{st}/2\textsuperscript{nd}/3\textsuperscript{rd} trimester), peri-natal or post-natal (if known) |

**Pregnancy complications / concerns / exposures and time point (in weeks)**

| [] Intercurrent infection |
| [] Past medical/surgical Hx of Mother and foetus |
| [] Drug Hx – recreational and medication |
| [] Trauma Hx |
| [] Pregnancy induced hypertension (weight gain, increased BP, proteinuria) |
| [] Hyperemesis (severe morning sickness/pregnancy-related nausea) |
| [] Miscarriage/death of co-twin or triplet |
| [] Haemorrhage |
| [] Structural abnormalities in reproductive system e.g. incompetent cervix, bicornal uterus |
| [] Exposures – occupational risk |
| [] Assisted pregnancy |
| [] Preterm labour |
| [] Maternal diabetes |
| [] OTHER – |

### Family Pedigree (family history) – insert diagram or write notes

Example questions to ask family: any evidence of illness in the family on the maternal or paternal side; specifically any problems with development or intellect; presence of motor disorder, congenital deformity, decreased motor function over time, in-utero/death, disease
### Birth Details

<table>
<thead>
<tr>
<th><strong>Date lesion identified/diagnosed</strong></th>
<th><strong>COMMENTS</strong></th>
<th><strong>Date Mother received diagnosis (if known)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age lesion identified/diagnosed</strong></td>
<td></td>
<td><strong>Age of infant at diagnosis</strong></td>
</tr>
<tr>
<td><strong>Mother’s name at delivery</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hospital of birth</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mode of delivery</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Gestation at birth</strong></td>
<td></td>
<td><strong>Gestational age - time between the first day of the last menstrual period and the date of birth</strong></td>
</tr>
<tr>
<td><strong>Plurality (No. of pregnancies)</strong></td>
<td></td>
<td><strong>M = miscarriage</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>G = pregnancy</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>P = delivery</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>e.g. M1 G2 P1</strong></td>
</tr>
<tr>
<td><strong>Order</strong></td>
<td></td>
<td><strong>Birth order</strong></td>
</tr>
<tr>
<td><strong>Birth weight</strong></td>
<td></td>
<td><strong>Kg</strong></td>
</tr>
<tr>
<td><strong>Apgar scores</strong></td>
<td></td>
<td><strong>x @ 1min and x @ 5mins</strong></td>
</tr>
<tr>
<td><strong>Weight at discharge</strong></td>
<td></td>
<td><strong>Kg</strong></td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
<td><strong>Caucasian</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>European</strong></td>
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<tr>
<td></td>
<td></td>
<td><strong>Asian</strong></td>
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<tr>
<td></td>
<td></td>
<td><strong>African</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Hispanic</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Indigenous</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Other</strong></td>
</tr>
<tr>
<td><strong>Head circumference – birth (cm)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Head circumference – current (cm)</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Co-morbidities

<table>
<thead>
<tr>
<th><strong>Neonatal seizures</strong></th>
<th><strong>COMMENTS</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes/ no</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Infantile spasms</strong></th>
<th><strong>COMMENTS</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes / no</td>
<td>Infantile spasm – a specific type of spasm (symmetrical, axial)</td>
</tr>
<tr>
<td>Controlled/ not controlled</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Epilepsy</strong></th>
<th><strong>COMMENTS</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>Yes (defined by 2 unprovoked seizures excluding febrile or neonatal seizures)</td>
</tr>
<tr>
<td></td>
<td>If yes, still on medication, Yes/ No</td>
</tr>
</tbody>
</table>
### Seizure type
- Date of commencement of seizures
- Type observed:
  - *Generalised* or *partial*
  - *Generalised* – sudden onset of seizures that compromises responsiveness and affects the whole body
  - *Partial* – seizures have focality therefore symptoms reflect onset in 1 part of the brain

### Medications
- Yes/ no/ not applicable

### Visual impairment
- Normal
- Impaired
- Severely impaired (blind or no useful vision)

### Hearing impairment
- Normal
- Impaired
- Severely impaired (hearing loss > 70 dB)

### Body weight
- kg / percentile

### Body height
- cm / percentile

### Method of nutrition and age (in weeks)
- Oral
- Tube – nasogastric
- PEG (percutaneous endoscopic gastrostomy)

Note if fed orally/nasogastric tube/PEG partially or entirely.
### Health Issues

<table>
<thead>
<tr>
<th><strong>Respiratory Health</strong></th>
<th><strong>COMMENTS</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>No. days ventilated</td>
<td></td>
</tr>
<tr>
<td>No. days on oxygen</td>
<td></td>
</tr>
<tr>
<td>No. of hospitalisations for <em>chest infections</em> in the past 6 months (since last visit)</td>
<td></td>
</tr>
<tr>
<td>No. of episodes of <em>pneumonia</em></td>
<td></td>
</tr>
</tbody>
</table>

**Asthma**

Yes/ No

**No of episodes of asthmatic attacks** in the past 6 months (since last visit)

<table>
<thead>
<tr>
<th><strong>Examination findings</strong></th>
<th><strong>Clinical signs and symptoms</strong></th>
</tr>
</thead>
</table>

### Other Medical issues

<table>
<thead>
<tr>
<th><strong>List/describe and include any medications</strong></th>
</tr>
</thead>
</table>

### Additional Information

<table>
<thead>
<tr>
<th><strong>MRI</strong></th>
<th><strong>COMMENTS</strong></th>
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</thead>
<tbody>
<tr>
<td>- yes/no</td>
<td>Date and location of MRI (if applicable). If yes, need copy of report.</td>
</tr>
<tr>
<td>- date</td>
<td></td>
</tr>
<tr>
<td>- location</td>
<td></td>
</tr>
<tr>
<td>- copy of report</td>
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</table>

<table>
<thead>
<tr>
<th><strong>Cranial Ultrasound</strong></th>
<th><strong>COMMENTS</strong></th>
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<tbody>
<tr>
<td>- yes/no</td>
<td>Date and location of cUS (if applicable). If yes, need copy of report.</td>
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<tr>
<td>- date</td>
<td></td>
</tr>
<tr>
<td>- location</td>
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</tr>
<tr>
<td>- copy of report</td>
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<table>
<thead>
<tr>
<th><strong>Surgery</strong></th>
<th><strong>COMMENTS</strong></th>
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</thead>
<tbody>
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<td>Date, location and details of previous Surgery (if applicable)</td>
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</tr>
<tr>
<td>- location</td>
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</tr>
<tr>
<td>- details</td>
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</table>

<table>
<thead>
<tr>
<th><strong>Cranial Nerves</strong></th>
<th><strong>Notes</strong></th>
</tr>
</thead>
</table>
### External Support

<table>
<thead>
<tr>
<th>Service</th>
<th>COMMENTS</th>
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</thead>
<tbody>
<tr>
<td>Neonatologist</td>
<td>If no, refer to..</td>
</tr>
<tr>
<td>- yes/no</td>
<td></td>
</tr>
<tr>
<td>- name</td>
<td></td>
</tr>
<tr>
<td>- location</td>
<td></td>
</tr>
<tr>
<td>- contact info</td>
<td></td>
</tr>
<tr>
<td>Paediatrician</td>
<td>If no, refer to..</td>
</tr>
<tr>
<td>- yes/no</td>
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<tr>
<td>- name</td>
<td></td>
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<td>- location</td>
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<tr>
<td>- contact info</td>
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</tr>
<tr>
<td>Neurologist</td>
<td>If no, refer to..</td>
</tr>
<tr>
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<td>- location</td>
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<td>- contact info</td>
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</tr>
<tr>
<td>Occupational Therapist</td>
<td>If no, refer to..</td>
</tr>
<tr>
<td>- yes/no</td>
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<td>- name</td>
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<td>- location</td>
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<td>- contact info</td>
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<td>Occupational Therapy</td>
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<td>- timeframe</td>
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<td>- duration</td>
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<td>Physiotherapist</td>
<td>If no, refer to..</td>
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<td>Other(s)</td>
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<tr>
<td>- duration</td>
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<tr>
<td>Medical Report</td>
<td>If yes, need copy of report.</td>
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<td>- location</td>
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<td>- contact info</td>
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</tr>
</tbody>
</table>
9.22. Study documents – Medical History Update Checklist at 6 months
### UP-BEAT Study – Medical History Update
#### 6 months

**Medical Appointments over last 6 months**

<table>
<thead>
<tr>
<th>Who?</th>
<th>How frequently?</th>
<th>Location?</th>
<th>Follow-up?</th>
</tr>
</thead>
</table>

**Allied Health Appointments over last 6 months**

<table>
<thead>
<tr>
<th>Occupational Therapist</th>
<th>Occupational Therapy</th>
<th>Physiotherapist</th>
<th>Physiotherapy</th>
<th>Other(s)</th>
<th>Follow-up?</th>
<th>Missing data from initial medical questionnaire?</th>
</tr>
</thead>
<tbody>
<tr>
<td>- yes/no</td>
<td>- timeframe/frequency</td>
<td>- yes/no</td>
<td>- timeframe/frequency</td>
<td>- discipline</td>
<td>- yes/no</td>
<td>- timeframe/frequency</td>
</tr>
<tr>
<td>- name</td>
<td>- duration</td>
<td>- name</td>
<td>- duration</td>
<td>- name</td>
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<td>- contact info</td>
<td></td>
<td>- contact info</td>
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</table>

What? How often/duration? Compliance?
9.23. Study documents – Medical History Update Checklist at 12 months
### UP-BEAT Study – Medical History Update

**12 months**

<table>
<thead>
<tr>
<th>Medical Appointments over last 6 months</th>
<th>Who?</th>
</tr>
</thead>
<tbody>
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<td></td>
<td>How frequently?</td>
</tr>
<tr>
<td></td>
<td>Location?</td>
</tr>
<tr>
<td></td>
<td>Follow-up?</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Allied Health Appointments over last 6 months</th>
<th>Occupational Therapist</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>- yes/no</td>
</tr>
<tr>
<td></td>
<td>- name</td>
</tr>
<tr>
<td></td>
<td>- location</td>
</tr>
<tr>
<td></td>
<td>- contact info</td>
</tr>
<tr>
<td>Occupational Therapy</td>
<td>- timeframe/frequency</td>
</tr>
<tr>
<td></td>
<td>- duration</td>
</tr>
<tr>
<td></td>
<td>- group/individual</td>
</tr>
<tr>
<td></td>
<td>- home program: Y/N</td>
</tr>
<tr>
<td></td>
<td>What? How often/duration?</td>
</tr>
<tr>
<td></td>
<td>Compliance?</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Physiotherapist</th>
</tr>
</thead>
<tbody>
<tr>
<td>- yes/no</td>
</tr>
<tr>
<td>- name</td>
</tr>
<tr>
<td>- location</td>
</tr>
<tr>
<td>- contact info</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Physiotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>- timeframe/frequency</td>
</tr>
<tr>
<td>- duration</td>
</tr>
<tr>
<td>- group/individual</td>
</tr>
<tr>
<td>- home program: Y/N</td>
</tr>
<tr>
<td>What? How often/duration?</td>
</tr>
<tr>
<td>Compliance?</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- discipline</td>
</tr>
<tr>
<td>- name</td>
</tr>
<tr>
<td>- location</td>
</tr>
<tr>
<td>- contact info</td>
</tr>
<tr>
<td>- timeframe/frequency</td>
</tr>
<tr>
<td>- duration</td>
</tr>
<tr>
<td>- group/individual</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Follow-up?</th>
</tr>
</thead>
</table>

| Missing data from initial medical questionnaire? |
9.24. Study documents – Study Checklist for each participant’s chart
UP-BEAT STUDY Checklist

Baby’s Name__________________ DOB.______________ Code No.______________

Pre-assessment

<table>
<thead>
<tr>
<th>Activity</th>
<th>Sent</th>
<th>Returned</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening by phone / interview/ email</td>
<td>yes/no</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Participant Information form</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consent forms - study</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Media Consent</td>
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</tbody>
</table>

Assessment

<table>
<thead>
<tr>
<th>Home Visit 1: 9 weeks</th>
<th>Due Date</th>
<th>Completed</th>
<th>Downloaded</th>
<th>Scored</th>
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</thead>
<tbody>
<tr>
<td>General Movements</td>
<td>GM</td>
<td>GM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Imitation Assessment (2 cameras)</td>
<td>IA</td>
<td>IA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parent training, set up training &amp; video</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phone call : 1-2 days post 1st visit</td>
<td></td>
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<td>Reaching and Grasping Assessment (chair)</td>
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<tr>
<td>Infant Hand Assessment</td>
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<td>Collect video equip &amp; toys</td>
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UP-BEAT STUDY Checklist (cont’d)

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**Home Visit 4: 16 weeks**
- General Movements
- Reaching and Grasping Assessment
- Infant Hand Assessment

**Home Visit 5: 18 weeks**
- General Movements
- Reaching and Grasping Assessment
- Infant Hand Assessment

**RCH 6mths**
- Infant Hand Assessment
- Bayley III
- EEG

**RCH 12 mths**
- Bayley III