**RESEARCH STUDY PROTOCOL**

**Peer delivered early intervention for infants at high risk of cerebral palsy/ neurodevelopmental disability in Indigenous Australia**

**Learning through Everyday Activities with Parents Study**

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**Background:**

Indigenous children and those living in rural/ remote and disadvantaged communities have an increased risk of neurodevelopmental disabilities (NDD), including cerebral palsy (CP), foetal alcohol spectrum disorder (FASD) and minor neurological disorder.1 2 Cerebral palsy (CP) is the most common childhood physical disability (1 in 700 Australians), with post-natally acquired CP **five times more likely in Indigenous Australians**.2 The rates of FASD and NDD in remote Indigenous communities have been reported **among the highest globally in up to a third of children**.1 Children in these contexts may have greater biological and psychosocial risk factors, including increased rates of central nervous system injury and infection, chronic illness, psychosocial deprivation, and prenatal alcohol exposure.3 4

The **first 1000 days** of a baby’s life are now well understood to lay a **critical foundation for the individual’s lifelong trajectory**.5 It is therefore essential that infants at-risk of CP/ NDD are identified early to enable early targeted motor and cognitive training to stimulate the postnatal brain and musculoskeletal development.6 7 Our international clinical practice guideline has recommended that reliable detection of infants at risk of CP should occur from 12 weeks corrected age. However, families living in remote locations often do not receive diagnosis or intervention until after the child’s second birthday; missing a significant window of neuroplasticity. To identify these at risk infants and their parents, we need to implement simple affordable community surveillance models, and establish pathways to link high risk infants to local accessible evidence-based interventions. The lay health worker model has been highly effective in Indigenous, cross-cultural and hard to reach contexts, providing a novel service delivery model to improve intervention access, community empowerment and sustainability.

The Learning through Everyday Activities for Parents program (LEAP) represents a paradigm shift for the provision of evidence-based interventions for infants at high risk of CP/ NDD in rural/ remote and Indigenous communities in Australia. This novel approach delivered through Indigenous Allied Health Workers (IAHW) provides a viable and scalable solution tailored to this context.

**LEAP** is delivered early. It is a proactive approach to support families before challenges arise.

**LEAP** is delivered by **members of the local community** for their own community, allowing all Australian children to reach their potential.

**LEAP** supports the parent within their family/community context, and focuses on the family unit.

**Sites:**

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| **Organisation** | **Communities** |
| Cairns and Hinterland Hospital and Health Services District | Referral Centre for communities of Far North Queensland |
| Apunipima Cape York Health Council | Aurukun, Coen, Hope Vale, Kowanyama, Laura, Lockhart River, Mapoon, Mossman Gorge, Napranum, Pormpuraaw, Wujal Wujal |
| Torres Strait |  |
| Yarabah |  |
| Mamu |  |
| Mulungu |  |
| Wuchopperen |  |

**AIMS AND HYPOTHESES**

**Aim 1**: To determine the efficacy of a peer-to-peer multi-domain early intervention (LEAP-CP) on motor outcomes in Indigenous infants at high risk of CP.

***H1****: Indigenous infants with CP who receive the LEAP-CP intervention will have better motor development on the Peabody Developmental Motor Scales compared to infants receiving care as usual.*

**Aim 2:** To determine the efficacy of a peer-delivered multi-domain culturally adapted early intervention (LEAP-CP) on caregiver’s mental health outcomes.

***H2:*** *Caregivers who receive LEAP-CP intervention will have reduced depression and anxiety scores on the Depression, Anxiety and Stress Scale compared to those receiving care as usual.*

**Aim 3:** To implement early detection of Indigenous infants at high risk of CP, through targeted training of clinicians and community workers using the General Movements assessment via the GMApp and the Hammersmith Infant Neurological Examination.

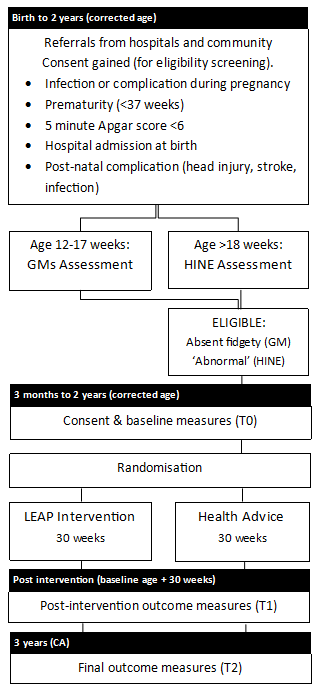
***H3:*** *The age of detection of “high risk of CP” will be reduced to <9 months corrected age.*

**PURPOSE:**

The LEAP-CP program presents a feasible and scalable service delivery model, with potential to improve the developmental trajectories of Indigenous infants with CP, their caregivers and broader family unit. Healthy families lead to healthy communities. This program will implement new International Clinical Practice Guidelines to reduce the age of detection of infants at high risk of CP to <9 months. Indigenous families are less likely to seek a diagnosis for their child until an overt disability is evident,2 and face barriers to accessing regular and culturally sensitive services. As a consequence, children with CP from Indigenous Australia frequently miss a significant window of opportunity for improved attachment, developmental and health outcomes. The proposed LEAP-CP program, a community-based intervention tailored to community needs, is uniquely delivered peer-to-peer in the home, presenting a viable and sustainable solution.

**RESEARCH PLAN**

**Study Design**: This is a randomised, single-blinded controlled multisite trial, informed by the CONSORT guidelines (Figure 1).

**Study Setting**: Primary recruitment sites will target communities around the Cape, Cairns, Townsville, Rockhampton/ Central Queensland, and South East Queensland. The Far North Queensland site will identify infants through the Cairns and Hinterland Hospital and Health Service, and partner with Aboriginal Controlled Community Health Organisations for the delivery of the program in community.

**Study Period**: This study will commence recruitment in June 2019 and conclude recruitment in June 2023.

**Informed consent:**

Potential participants will be identified by their treating clinician, and provided with a study flyer and verbal information about the study (this may be during the hospital stay, or through ante-natal care in the community). Flyers and information sheets regarding the study will also be circulated within referral centres (Health and Aboriginal Community Controlled). Permission will be sought from the caregiver/ legal guardian to have their infant’s details and contact details passed on to either/ both the (i) local medical team; (ii) the research team (this permission can be granted concurrently or staged). The community health worker (in community) will have the initial discussions with the family about the study, based on the consent information sheet. Once permission has been given for their details to be provided to the research team, a researcher will identify a time to call the family to clarify the information statement, answer further questions and gain consent, with the health worker present to assist in translation and/ or cultural interpretation. If the family consents to screening, the primary worker will support the family through this process (describing the assessment, conducting the assessment, communicating the results), supported as necessary by the primary medical team. If the result is ‘high risk of NDD’ the same worker will discuss the intervention program and determine the family’s interest in ongoing participation.

**Fig 1. CONSORT Flow Diagram**

This research recognises the major values of Aboriginal and Torres Strait Islander People with regard to health research in its design and conduct. The NHMRC guidelines have been implemented as follows:

Reciprocity and Community Engagement: the researchers will consult with the elders in the local community region. This will be conducted through the local ATSI liaison officers.

Respect: All flyers and information sheets for families will be prepared as culturally sensitive to ATSI families and communities as well as being sensitive to the needs and environment of rural and urban settings and communities, with respect to the different living practices, history and how that might impact on the ATSI family.

Equality: all ATSI families will have equal access to all medical services and their involvement or non-involvement

in the research will in no way impact upon this access to medical services.

Responsibility: the research team has read the guidelines from the NHMRC on ethical conduct of ATSI Health Research and has responsibility to the family to provide a positive hospital experience taking account of the cultural needs of the family. Where ATSI families seek additional support during the recruitment process we would organise for an ATSI liaison officer to be present during the initial consultation and explanation of the study and at any further follow up as required.

Survival and protection: The comprehensive therapy provided by the current study will assist the long term health and quality of survival of these children. The research team will follow the usual QLD Health guidelines for reporting child protection issues.

**Study Subjects:**

Infants eligible for screening will be those with pregnancy complications, born preterm (born <37 weeks' gestation), term with neonatal encephalopathy, 5 minute Apgar <6, history of neurological risk factors (e.g., congenital disabilities, small for gestational age, seizures), or post-natal complications (head injury, stroke, infection).

*Inclusion/ Exclusion Criteria:*

Following screening, 86 infants aged 3 months to 2 years corrected age with one or both parents identifying as Aboriginal or Torres Strait Islander will be recruited. Infants must be assessed as ‘high risk of CP or NDD’ or have a confirmed diagnosis of CP. Infants are determined to be high risk of CP/ NDD if assessed as:

1. ‘Abnormal’ neuroimaging results associated with a motor disability including an abnormality in one or more of the following structures: sensorimotor cortex, basal ganglia, posterior limb of the internal capsule.
2. ‘Absent fidgety’ on General Movements for infants aged 12-17 weeks;
3. ‘Abnormal’ (score<56 at 3m, <59 at 6m, <73 at 9-24m) on the Hammersmith Infant Neurological Examination (90% predictive of CP) if aged >18 weeks.8
4. The Rapid Neurodevelopmental Assessment will also be conducted to use in concurrent and predictive validity data for other disabilities.

Infants with complex medical conditions requiring acute medical care will be excluded.

**Randomisation and blinding:** Families will be randomised using central concealed random allocation to receive either LEAP-CP or care as usual. Randomisation will be computer generated through a REDCap database (online). Eligibility and baseline assessments will be completed prior to randomisation. All study participants, including caregivers, Community Disability Workers administering intervention, researchers assessing the outcomes and analysing the data will be masked to group allocation.

**Intervention:**

*LEAP-CP Intervention:* The LEAP-CP intervention is a multi-domain best practice intervention consisting of infant goal-directed training, learning games, and caregiver educational modules, based on efficacy shown in systematic reviews9-12 and early intervention trials.13 14 The components shown necessary for effective interventions for infants with CP include (i) goal-directed tasks; (ii) home-based delivery9, (iii) responsive parenting; and include (iv) active motor learning and (iv) enriched environments.10 LEAP-CP is based on a parent coaching model which promotes caregiver problem solving and self-determination. Specifically, LEAP-CP includes:

* **Goal-directed skill training** includes motivating infant-generated activities practiced to optimise learning; using principles of structure, repetition, and variation.15 Functional motor skills, such as reach/ grasp and attaining anti-gravity postures, will be coached, and parents given visual supports (photo/ video) for ongoing practice through the week.
* **Responsive parenting and environmental enrichment**. This is based primarily on the PACT model (Parenting Acceptance and Commitment Therapy) developed by CIE16, and resources based on the Abecedarian curriculum modified for CP.10 17 The Abecedarian approach has strong empirical evidence from >16 RCTs in at-risk children.17 This includes early play-based learning (cognitive, motor and sensory) and literacy resources.
* Parent educational modules: These evidence-based discussion topics cover three broad areas: (i) **‘learn’** – enabling active play with cognitive challenge for babies with CP18; (ii) **‘grow’** – feeding, nutrition (breastfeeding, complementary feeding, balanced diet) and health19; (iii) **‘love’** caregiver mental health based on acceptance and commitment therapy and responsive parenting.

*Care as usual arm:* Care as usual consists of the routine primary and allied health programs provided in the community, in addition to specific post-natal health advice programs (eg first 1000 days programs). Care as usual will be documented on the health resource use form. If there are no routine post-natal programs delivered in the community, a basic health advice program will be delivered once per month (7 visits) by a community health worker, based on the World Health Organisation’s Integrated Management of Childhood Illness Key Family Practices. This includes counselling on breastfeeding and introduction of complementary nutrition, hygiene practices, vaccination counselling, and management of the sick child.

*Peer to Peer Service Delivery:* A centralised allied health coordinator will collaborate with the Indigenous Allied Health Worker and Regional Team Leaders on the program content on a monthly schedule utilising online telehealth facilities. Community Disability Workers are peer trainers who are employed for each community area. Indigenous Allied Health Workers will instruct the caregiver (or other significant people in the infant’s life) on the intervention weekly in the home. Caregivers are the primary change agent, encouraged to do the intervention with their infant daily during the week (incremental dose from 20-40 minutes, to a total of 104.2 hours over 30 weeks). Use of a peer-delivered service delivery model ensures cultural relevance, long-term sustainability and empowerment of caregivers.

*Adverse Events*: The LEAP-CP intervention is considered to be safe, with no additional risks for participants. Any risks associated with kinship or relationships within community will be monitored by the regional team leader at monthly supervision, and discussed with the research team if indicated. Any serious adverse events such as injury, prolonged hospitalisation or mortality occurring during program delivery will be monitored by the Data Safety Monitoring Representative, a non-treating senior medical professional. They will review study retention, compliance/quality of treatment and monitor any adverse or unintended effects on a 12 monthly basis and advise the Chief Investigators regarding whether the adverse events are likely related to the intervention provided in the trial.

**OUTCOME MEASUREMENT:**Outcomes will be assessed by a researcher masked to intervention arm, pre-intervention (T0), post-intervention (T1) and at 3 years (T2).

**Primary Child Outcome Measurement:**

* The child’s motor outcomes will be assessed using the **Peabody Developmental Motor Scales – 2nd edition (PDMS-2)**, a commonly used measure of motor skills in infants and children aged birth to 6 years. It has demonstrated validity and responsiveness in infants with CP.13
* The **Canadian Occupational Performance Measure (COPM)** will be used to measure parent-perceived change in their child’s performance of the goal and their own satisfaction with progress.20

**Primary Caregiver Outcome**

* The **Depression, Anxiety, Stress Scale – Short Form (DASS)** is a 21 item self-report questionnaire reflecting the frequency or severity of the caregiver’s experiences with depression, anxiety and stress over the past week. It has high internal consistency (α=0.83, 0.78 and 0.87 for depression, anxiety and stress respectively (Norton, 2007). High convergent validity has been established between the DASS and other measures of similar constructs: DASS depression scale and the Beck Depression Inventory *(r*= 76), DASS anxiety scale and the Beck Anxiety Scale (*r= .74)* and DASS stress scale and the Positive and Negative Affect Schedule (*r*= .74).21

*Secondary Child Outcome Measures:* *Goals and functional outcomes:*

* The child’s cognitive and communication outcomes will be assessed using the **Bayley Scales of Infant Development III (BSID-III)**, the gold standard norm-referenced assessment of infant development (0-3 y).22
* The child’s functional outcomes in self-care, mobility and social function will be assessed using parent-report on the **Pediatric Evaluation of Disability Inventory – Computer Adaptive Test (PEDI-CAT)**. The PEDI-CAT has been Rasch-analysed in children with disabilities and typical development. Raw scores will be converted to standardised scores (0-100).23
* **Near Detection Scale (NDS)** is a 10-point vision assessment of visual fixation on graded standardised lures viewed at near distance (30cm), ranging from no light perception (0) to 1.2cm ‘lure’ (yellow candy presented on a dark green/ black cloth).24
* **Nutritional status** will be determined using length/ height and weight which will be converted to z scores using the World Health Organization age and gender referenced data.25

*Secondary Child Outcome Measures:* *Other child outcomes*

* The **Emotional Availability Scale** (EAS)26 27 is a 20-minute observation of the parent-infant relationship. The parent-infant observation will be a naturalistic observation of a parent-infant interaction in the family’s own home. The IAHW will assist parents to record the interaction, using a recording device of their own or supported by the community worker. The EAS measures the quality of the relationship itself across six scales: parental sensitivity, parental structuring, parental non-intrusiveness, parental non-hostility, child responsiveness and child involvement. The scale has high inter-rater reliability for parental responsiveness (.96), involving (.87), sensitivity (.93) and structuring (.76).
* **Home Observation for Measurement of the Environment (HOME) Inventory: Infant and Toddler Version** is a measure of the quality and quantity of parent and home stimulation, covering six domains of parent responsivity, acceptance, and involvement; and the home physical environment including availability of learning materials, and variety of stimulation.28
* **The** **Infant Toddler Social Emotional Assessment (ITSEA) at T1 and T2**: The ITSEA is a 92-item parent-report checklist of the child’s adaptive behaviours (e.g. attention, ability to sleep). The ITSEA has been shown to be responsive to improvements from home-based parent-infant intervention. It has strong test-retest reliability (α=.75-.91) and concurrent/discriminant validity.
* **The Infant Toddler Quality of Life Questionnaire™ (ITQOL-SF47)**: The ITQOL was developed for use in infants and toddlers 2 months - 5 years. The ITQOL short form measures quality of life across physical, mental and social well-being. The test has 47 items in the short-form and is completed by parent-report. For each of the 47 concepts, item responses are scored, summed, and transformed to a scale from 0 (worst health) to 100 (best health).

*Co-variates and descriptive measures:* These variables will be used to describe the groups and used as covariates in the analysis:

* **Physician checklist** (T0): This checklist gathers birth and developmental history from the caregiver, and was developed by our team for a large population-based study in Australia.29 Questions include preterm status, birth complications, presence of seizures and medications.
* **Rapid Neurodevelopmental Assessment** (T0) will be used to determine functional status in the following domains: primitive reflexes, gross motor, fine motor, vision, hearing, speech, cognition, behaviour and seizures. This will provide concurrent validity with the GMs and HINE, and diagnostic accuracy data for improving early screening of other developmental domains.
* **Magnetic resonance imaging (MRI):** When available, clinical neuroimaging will be retrieved to undertake semi-quantitative scoring.30 Structural MRI will be evaluated by a paediatric neuroradiologist masked to clinical features and history, for type of lesion, and to describe a presumed pathogenic pattern (e.g. stroke, hypoxia/anoxia, toxic, metabolic or infective). The brain lesion severity will be determined by using the Fiori semi-quantitative scale,31 a valid and reliable measure of brain lesion severity (location, extent, depth) in children with CP.
* **Differential diagnosis at 36 months C.A.** will be provided by a qualified paediatrician according to published guidelines, based on clinical history (on the Physician Checklist), brain imaging as available, and videoed HINE and Gross Motor Function Classification System semi-structured play session. Standard frontal and oblique photographs will also be taken and analysed with the Face2Gene application for facial dysmorphology assessment.32
* **Gross Motor Function Classification System (GMFCS)** (T1, T2)**:** internationally recognised five-level classification of children’s gross motor function.33
* **The Manual Abilities Classification System for Infants (mini-MACS)** (T1, T2) the gold standard for classifying infant’s ability to handle objects in daily activities.34
* **Motor type** (spasticity, dyskinesia, hypotonia) **and distribution** (number of limbs) (T1, T2) will be classified by a physiotherapist/ physician according to the Surveillance of CP in Europe.35
* **Paediatric Rehabilitation Intervention Measure of Engagement – Service Provider (PRIME-SP)** (T1) will be completed by the Indigenous Allied Health Worker as a measure of family engagement with the program.
* **Health Economics:** A within trial cost-utility analysis29 will be conducted to synthesize the costs and benefits of the LEAP-CP training program. Resource use (staff time, equipment and facility use) associated with the program will be collected alongside the RCT. Health care utilization will be collected using a resource use questionnaire previously used in CP. Utility will be derived from the ITQoL, a quality of life utility measure validated in an Australian population36. AI Byrnes will provide expertise in developing economic models to analyse costs and outcomes of the LEAP-CP intervention. Incremental Cost Effectiveness Ratios (ICERs) will be estimated and sensitivity analyses undertaken as undertaken to appropriately reflect uncertainty in the results as undertaken in previous RCTs by our group50.

**Sample size:** Based on pilot data from the GAME RCT,13 there was an effect size of 0.5 on the PDMS-2. The present study recruits children with limited access to treatment, and as such the intervention is expected to result in greater improvement than the GAME trial. A total of 39 children/ group will enable an effect size of 0.65 on the PDMS-2 to be detected with 80% power (α=0.05). Accounting for 10% attrition, this equates to a total of 86 infants (n=43/group). The LEAP-CP intervention t final outcome compared to care as usual.

**Analysis:**Between group differences for the primary outcome measure (PDMS-2 raw score; continuous data) will be compared using linear regression analyses. The between-group differences at baseline for key characteristics (age, gender, epilepsy, GMFCS, motor type, preterm status) will be calculated, and if any characteristics differs at p<0.01 it will be included as a covariable in all regression models. The sample will be stratified by age (<12 months/ >12 months) and neurological severity (HINE<40). Secondary analyses will consider gains on function (PEDI-CAT) or cognitive outcomes (BSID-III), and caregiver outcomes, and analysed similiarly. Analyses will be conducted on an intention to treat basis. No imputation of missing data will occur. Statistical significance will be set at p<0.05. A/Prof Mark Chatfield (Biostatistics) will provide expert advice on the analysis.

**OUTCOMES AND SIGNIFICANCE**

By intervening in the first year of life with the caregiver-infant dyad situated within the broader family and community context, the program is expected to improve infant developmental outcomes while simultaneously building the confidence, capacity and support of the caregiver and family. With the current roll-out of the National Disability Insurance Scheme, the Australian healthcare system requires new models of early detection and intervention for CP. Providing early, contextualised interventions in the home is expected to result in a model that is both feasible, sustainable and culturally appropriate. LEAP-CP has the potential to deliver important outcomes spanning several tiers of society, including infant, caregiver/ family; and health systems. It will overcome barriers of getting effective interventions to the right children at the right time. Improvements to children’s developmental trajectories are known to increase the likelihood of becoming valued and contributing community members. By empowering local community members as disability resource champions in their own communities, this intervention will have a lasting and far-reaching benefit, beyond the duration of the study. It will also provide important opportuntities for skill development and training of local Indigenous workforce (including the exploration of formal qualifications). Building on the peer-delivered model used in resource-poor contexts and Indigenous communities, this project is likely to result in a cost-effective and feasible model of care for infants with CP/ NDD that is highly scalable and transposable to other hard to reach populations.

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