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Study Protocol: Early detection of Australian Aboriginal and Torres Strait Islander infants at high risk of adverse neurodevelopmental outcomes at 12 months corrected age: LEAP-CP prospective cohort study

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ABSTRACT

Introduction Aboriginal and Torres Strait Islander infants may experience early life factors increasing their risk of developmental vulnerability which persist into later childhood, further compounding the health inequities experienced by First Nations peoples in Australia. The LEAP-CP prospective cohort study will investigate the early identification of adverse neurodevelopmental outcomes (NDO) in 'at risk' Aboriginal and Torres Strait Islander infants living in Queensland, Australia. Diagnostic accuracy and feasibility of early detection tools for identifying infants 'at risk' of a later diagnosis of adverse NDO or neurodevelopmental disorder (NDD) will be determined.

Methods and Analysis Aboriginal and/ or Torres Strait Islander infants born in Queensland (birth years 2020-2022) will be invited to participate. Infants aged ≤9 months corrected age (CA) will undergo screening using the: (i) General Movements Assessment (GMA); (ii) Hammersmith Infant Neurological Examination (HINE); (iii) Rapid Neurodevelopmental Assessment (RNDA) and (iv) Ages and Stages Questionnaire - Aboriginal adaptation (ASQ-TRAK). Developmental outcomes at 12 months CA will be determined for: (i) neurological (HINE); (ii) motor (Peabody Developmental Motor Scales 2); (iii) cognitive and communication (Bayley Scales of Infant Development III); (iv) functional capabilities (Pediatric Evaluation of Disability Inventory - computer adaptive test); and (v) behaviour (Infant Toddler Social and Emotional Assessment). Infants will be classified as typically developing or 'at risk' of an adverse NDO and/or specific NDD based on symptomology using developmental and diagnostic outcomes for (i) CP (ii) ASD and (ii) FASD. The effects of perinatal, social and environmental factors, caregiver mental health and clinical neuroimaging on neurodevelopmental outcomes will be investigated.

Ethics and Dissemination Ethics approval has been granted by appropriate Queensland ethic committees with governance and support from local First Nations communities. Findings from this study will be disseminated via peer-reviewed publications and conference presentations.

Trial registration number ACTRN12619000969167

Key words: Indigenous, Aboriginal and Torres Strait Islander, infant, prospective cohort study, clinical assessment tools, neurodevelopmental outcomes, neonatal screening, cerebral palsy, autism spectrum disorder, fetal alcohol spectrum disorder

Strengths and limitations of this study:

- This prospective population-based cohort study investigates the use of standardised screening tools to predict a later diagnosis of adverse neurodevelopmental outcomes in an Australian Aboriginal and Torres Strait Islander birth cohort.
- This study aims to implement early screening programmes for Aboriginal and Torres Strait Islander infants via targeted training of local clinicians to identify infants 'at risk' of adverse neurodevelopmental outcomes early and fast track infants and families to early intervention services.
- Findings of this study will inform culturally sensitive practice, including adapted resources and accepted screening tools, enabling clinicians to select both clinically meaningful and culturally appropriate tools to identify Indigenous infants 'at risk' of a later diagnosis of adverse neurodevelopmental outcomes and/or Neurodevelopmental Disorder.
- The remote locality of many Indigenous communities in Australia may present challenges, limiting access to health services and impacting loss to follow-up of infants at study outcome timelines.

INTRODUCTION

In Australia, Aboriginal and Torres Strait Islander peoples, are among the most disadvantaged across all domains. In acknowledgement of the unique and distinct countries, cultures and languages of Australian First Nations people, the term 'Indigenous' is respectfully used herein to encompass but not homogenise the diverse identities of Aboriginal and Torres Strait Islander peoples.

Ongoing intergenerational trauma, systematic displacement from traditional lands, loss of culture and racism experienced by Australian Indigenous people continues to manifest in socio-economic disadvantage, marginalisation, reduced education and employment opportunities, leading to poorer health outcomes[1,2]. Indigenous Australians are 1.8 times more likely to experience disability, twice as likely to have a severe disability and are less likely to access support[3] compared to non-indigenous Australians[4,5]. Inequities in access to culturally safe health and disability support services[6], long waiting lists and the rurality of some Indigenous communities, further compounds this disadvantage[7,8]. These factors have contributed to a significant gap in health outcomes between Indigenous and non-Indigenous Australians[3,9].

Indigenous children, living in urban, rural and remote Australia, have an increased risk of adverse Neurodevelopmental Outcomes (NDO). This can include being at risk for a range of specific childhood neurodevelopmental disorders (NDD): Cerebral Palsy (CP), Fetal Alcohol Spectrum Disorder (FASD), and Autism Spectrum Disorder (ASD)[8,10,11]. These conditions are characterised by impaired development of the early central nervous system, resulting in cognitive and/or physical disability[12,13]. Indigenous children are 30% more likely to have a physical disability, and are at higher risk of developmental and intellectual difficulties, compared to non-Indigenous children[11,14,15]. The prevalence of NDDs in some remote communities are reported to be as high as 30% of the paediatric population[10].

Indigenous infant early life risk factors

Many Australian Indigenous infants can experience a range of perinatal, maternal, post-neonatal (PNN) and socioeconomic risk factors that increase their risk of later adverse NDOs. While the neonatal death rate for Indigenous infants has declined, the rates of preterm birth (i.e., <37 weeks GA), low birth weight (LBW; i.e., <2500g) and small for gestational age (SGA) births has remained relatively stable[16]. In 2018, infants of Indigenous mothers were 65 percent more likely to be born pre-term, 87 percent more likely to be LBW and 52 percent more likely to be SGA, compared to babies of non-Indigenous mothers[16]. In addition, 28 percent of Indigenous infants were admitted to the neonatal intensive care unit (NICU) or special care nursery (SCN), requiring specialised medical treatment[16].

Improving Indigenous birth outcomes, including preterm birth and LBW, is a national priority for the Australian Closing the Gap Agenda[17]. Infants born pre-term and with LBW have an increased risk of adverse NDOs, which can influence school readiness and academic achievement[18-22]. Biological and environmental risk factors impact birth outcomes and are associated with increased risk of developmental vulnerability[14,23-25]. These factors are compounded by remote locality, access to appropriate and culturally sensitive antenatal care, and, socioeconomic disadvantage[23-25]. Maternal factors including age, education, health,

smoking and substance use have been linked to poorer birth outcomes[14,24,25]. In Australia, Indigenous mothers are more likely to be younger, single, attain lower levels of education, live in lower socio-economic circumstances and have lower rates of attendance at antenatal care[16,25]. Emerging evidence demonstrates the protective impact of culturally led[26] birthing programs which have led to an improved uptake in antenatal care and smoking cessation, subsequently lowering the risk of neonatal and adverse developmental outcomes[26-29].

The cultural, geographical and socio-economic barriers to healthcare access experienced by Indigenous Australians can lead to delayed identification of infants at risk of adverse NDOs with subsequent delays in receiving early intervention to optimise outcomes[11,30]. While there is consensus that early detection is important for all adverse NDOs, variability exists in the recommendations for the screening and diagnosis of CP, ASD and FASD.

Neurodevelopmental Disorders (NDD)

NDDs are characterised by distinct clinical manifestations and symptomology. A transdiagnostic approach supports the notion that many NDDs share similar early markers and comorbidities across multiple neurodevelopmental domains[31-33]. Targeted early screening programs should aim to identify an infant's risk status for a range of adverse NDOs which may predict a later specific diagnosis[32,34]. Differences in quality of movement, atypical motor development, and cognition are common early risk attributes and neurodevelopmental features of CP, ASD and FASD[10,35-39].We hypothesise that valid and reliable predictive tools utilised for the detection of CP may also identify early neurodevelopmental vulnerabilities in infants at risk of a later diagnosis of ASD and FASD and/or other substantial developmental delays.

Cerebral Palsy (CP)

Cerebral Palsy, the most common physical disability of childhood (1 in 700 live births)[40], is defined as a developmental disorder of movement and posture attributed to non-progressive disturbances in the developing brain that occur in early infancy, impacting function, participation and self-care[41]. Injury to the developing brain can occur pre-, peri-, or post-neonatally, due to a recognised event associated with brain damage[8].

Improvements in medical care and neuroprotective interventions for preterm birth, LBW and other pregnancy complications have been associated with a decline in the overall rate of CP[42]. Advances in early detection, diagnosis, prevention and intervention in high resource countries have additionally led to improvements in CP prognosis and decreased incidence[42,43]. In Australia, the trend in declining CP rates has demonstrated a decrease in incidence from 1 in 500 children to 1 in 700 children and a reduction in severity of motor function, with more children ambulant[40,43].

International Clinical Practice Guidelines support a confirmed or 'high risk' of CP diagnosis prior to 6 months CA[44]; however the age of diagnosis of CP in high income countries still occurs relatively late, usually between 12 to 24 months, delaying access to early intervention services[44]. The use of gold standard clinical assessments, such as Prechtl's Qualitative Assessment of General Movements (GMA), the Hammersmith Infant Neurological

Examination (HINE) and Magnetic Resonance Imaging (MRI), are recommended for reliable and accurate prediction of 'high risk' of CP[44,45]. Individually these tools are highly sensitive, however a combined abnormal MRI and trajectory of abnormal GMA and HINE scores demonstrates the greatest diagnostic accuracy (97.8% sensitivity and 99.2% specificity) at 3 months CA[46]. The GMA evaluates the quality of an infant's early spontaneous movement patterns, which reflects central nervous system integrity and function[47,48]. An abnormal/absent GMA at 3 months CA is highly predictive of CP in 'high risk' infants[45], and may be a marker for other adverse NDOs[35,47,49-51]. Due to the time-sensitive nature of the GMA (at 11-17 weeks CA), the HINE is recommended to assess an infant's neurological development between 3-24 months CA[44]. The HINE also provides insight into CP topography (unilateral vs bilateral)[52,53] and severity (ambulant vs non-ambulant, GMFCS I-III vs IV-V)[54-58]. While the GMA and HINE are relatively easy to administer, trained clinicians are required to evaluate and interpret scores.

In Australia, the rate of CP is estimated to be 50 percent higher for Indigenous children[8], with the rate of pre- or perinatally acquired CP almost three times that of non-Indigenous infants[59]. Indigenous infants with CP are more likely to be born extremely pre-term (<28 weeks) and LBW than non-Indigenous infants with CP, increasing their risk of functional severity[8,60]. Indigenous infants are five times more likely to acquire CP post-neonatally, which is associated with an increased severity of CP and linked to socioeconomic conditions[8,23,40]. In addition to higher rates of CP diagnosis, Indigenous children with CP have poorer cognitive and gross motor outcomes and a higher proportion of comorbidities, being twice as likely to have visual impairments and 50 percent have a co-diagnosis of epilepsy[8,59]. Accurate Australian data pertaining to the prevalence of CP, age of diagnosis, rates of referral and access to early intervention in Indigenous infants remains unknown.

Autism Spectrum Disorder (ASD)

Autism spectrum disorder (ASD) describes a group of heterogeneous NDDs characterised by core difficulties with social interaction and the presence of restrictive and repetitive patterns of interest or behaviours[61]. Many individuals with ASD demonstrate associated impairments in cognition, challenging behaviours, communication and motor function[38,62]. With a 42 percent increase in prevalence from 2015 to 2018 in Australia[63] the diagnosis of ASD continues to be commonly made after two years and frequently not until school age (i.e. average six years;[64]), limiting timely early intervention[65].

Early motor abnormalities[38,39,66-68], reduced verbal skills, differences in social interactions[69,70] and ASD-related infant behaviours may be detected in children with ASD from 6 months CA; however, there are few ASD screening and diagnostic tools for infants <12 months of age[70,71]. The Autism Observational Schedule in Infants (AOSI) evaluates the presence of ASD-related behaviours, in infants aged 6-18 months[71-74]. Elevated AOSI scores at 12 and 18 months CA are associated with ASD diagnosis at 2 and 3 years of age, and are predictive of social-communication difficulties in high risk infants at 2 years[72-75]. Atypical responses to specific test items, including eye contact, social interest and orienting to name are discriminative between high risk infants with a subsequent diagnosis, high risk infants without subsequent diagnosis and low risk infants[74,76]. Differences in infant motor development[67,68,77] and the quality of early infant movements may provide additional

insights into ASD-related outcomes[35,47,51,78]. Studies investigating use of GMA for prediction of ASD in high risk infants, identified that >60 percent of children with a later confirmed diagnosis had abnormal or absent fidgety movements at 12-16 weeks of age[35,51,78]. Universal screening tools such as the Ages and Stages Questionnaire (ASQ;[79]) and the Rapid Neurodevelopmental Assessment (RNDA;[80]) identify infants with atypical cognitive, social and communication development, but require further investigation regarding the predictive ability of ASD-related behaviours.

There is a paucity of data relating to the prevalence of ASD in Australian Indigenous populations[81]. While some studies have investigated the incidence of ASD and intellectual disability among specific Indigenous communities, accurate prevalence remains relatively unknown, with reported inconsistencies impacted by differences in cultural conceptualisation of disability, misdiagnosis, and decreased awareness of ASD among Indigenous communities[3,15,64,81-84]. There is growing concern that Indigenous children are misdiagnosed or missing out on an ASD diagnosis[6,83], supporting the need for culturally sensitive early diagnostic tools and services.

Fetal Alcohol Spectrum Disorder (FASD)

Alcohol exposure in utero can result in adverse outcomes across multiple neurodevelopmental domains including: cognition, motor skills, brain structure, language, academic achievement, attention, and adaptive behaviour[85-87]. Fetal Alcohol Spectrum disorder (FASD) is the diagnostic term used for individuals who are exposed to alcohol prenatally and demonstrate severe impairment in 3 or more neurodevelopmental domains[86,88]. Diagnosis according to the Australian Guide is categorised as either; FASD with 3 sentinel facial features or FASD with < 3 sentinel facial features, indicating the presence or absence of facial dysmorphology specific to prenatal alcohol exposure (PAE) in the first trimester[86,87]. The co-existence of multiple comorbidities can complicate FASD diagnosis and further impact the long term sequalae[89]. FASD can be associated with an increased risk of physical health conditions[90], poor mental health, substance misuse, and involvement in the criminal justice system[91]. These lifelong consequences are extremely costly to the individual, family, health, education, disability and justice systems[92,93].

The Australian Guide to the assessment and diagnosis of FASD[88] recommends early intervention, however early diagnosis and provision of appropriate treatment strategies are under-developed[94]. In the absence of facial dysmorphology, there are few accurate early biomarkers for infants at risk of FASD[85,88,89,95]. Diagnostic assessments are complex, time consuming, and require a multidisciplinary team of specialised clinicians[87,96]. Furthermore, most of the recommended standardised neurodevelopmental assessments are for children >2 years[88]. The use of standardised screening tools <6 months CA, such as GMA and HINE may enable the accurate detection of neurodevelopmental delay, which could lead to earlier diagnosis of FASD.

The reported prevalence of FASD and patterns of PAE in Australia are variable, due to complexities with missed or misdiagnosis, practitioners not enquiring about prenatal alcohol use, and, availability of diagnostic services[94,96,97]. In Australia, rates of FASD in some Indigenous populations are among the highest globally, impacted by the interplay of biological and psychosocial risk factors[10,97,98]. In one remote community 19 percent of school-aged

children had a FASD diagnosis, 25 times higher than the global rate[98,99]. Furthermore, the prevalence of FASD (47 percent) among Aboriginal young people (13-17 years) in custody in WA is almost 6 times higher than that of non-Indigenous adolescents in custody[97]. The subsequent effect of PAE on developmental trajectory underpins the need for culturally sensitive, early screening tools to enable detection of infants who are high risk of FASD.

While there is emerging data on the prevalence and profile of adverse NDOs and NDDs in the Indigenous population[8,10,14,15,27,100] the focus has been on diagnosis of specific NDDs in early childhood. The aim of this cohort study is to investigate the use of early standardised screening tools (such as GMA, HINE) to determine risk status of infants aged ≤12 months CA, for a later diagnosis of CP, ASD, FASD and/or other substantial developmental delay in an 'at risk' Australian Indigenous birth cohort.

OVERVIEW OF AIMS

Broad Aim

The primary aim of the current study is to investigate the impact of early screening for Indigenous infants at risk of adverse NDOs due to prenatal, birth and early life factors, in terms of:

i. Diagnostic accuracy, clinical utility and cultural appropriateness of early infant neurodevelopmental assessments to accurately predict a later 'at risk' diagnosis at 12 months CA.
ii. Impact of perinatal variables, maternal factors and caregiver mental health on the developmental outcomes of Indigenous infants at risk of adverse NDOs in Queensland.

A comprehensive list of study aims and hypotheses are outlined in Table 1.

Table 1: LEAP-CP: Early detection study aims and hypotheses

AIM 1 To determine the predictive accuracy, of the General Movements Assessment (GMA), the General Movements Motor Optimality Score (MOS), the Hammersmith Infant Neurological Examination (HINE), the Rapid Neurodevelopmental Assessment (RNDA), and the Ages and Stages – aboriginal adaptation (ASQ-TRAK) to predict a later outcome at 12 months CA of 'at high risk' of (i) CP or (ii) Adverse Neurodevelopmental Outcome (non-CP) or (iii) Typically developing in Indigenous infants.	
H1a	Sensitivity to detect CP at 12 months CA in Indigenous infants will be >98% for abnormal GMA (Absent Fidgety, Abnormal Fidgety) at 3 months CA and >90% for suboptimal HINE score (<60 and/or ≥5 asymmetries) at 6 months CA.
H1b	Specificity to detect CP at 12 months CA in Indigenous infants will be >90% for abnormal GMA (Absent Fidgety, Abnormal Fidgety) at 3 months CA and >85% for suboptimal HINE score (<60 and/or ≥5 asymmetries) at 6 months CA.
H1c	Indigenous infants with a confirmed or 'at risk' diagnosis of CP at 12 months will have a motor optimality score (MOS) between 8 and 14 (GMFCS I-III) or <8 (GMFCS IV and V) at 3-5 months CA, infants with a diagnosis of 'at risk' of adverse NDOs (non-CP) at 12 months CA will have a MOS <21 at 3-5 months CA.
H1d	The sensitivity and specificity of the GMA and MOS to detect an adverse NDO (non-CP) at 12 months CA will be less than that of CP.

H1e	Sensitivity and specificity to detect adverse NDOs (non-CP) at 12 months CA will be ≥81% and ≥71% respectively for suboptimal HINE score (<65) at 6 months or (<70) at 9 months CA.
H1f	Indigenous infants who score 'at risk' on ≥1 domain the ASQ-TRAK at 6 months CA (domain specific cut offs gross motor<23, fine motor <26, communication<30, problem-solving<28, personal-social<26) will have a diagnosis of 'at risk' of adverse NDOs (non-CP) and/or CP at 12 months CA.
H1g	Indigenous infants who score moderate to severe on any domain of the RNDA at 6 months CA will have good to excellent specificity (>0.8) compared to poor to fair sensitivity (0.6-0.8) to detect 'at risk' of CP and/or adverse NDOs (non-CP) at 12 months CA.
AIM 2 To determine the neurological (HINE), motor (PDMS-2), cognitive (BSID-III), developmental (PEDI-CAT/ASQ-TRAK) and behavioural (ITSEA) profiles of Indigenous infants with a diagnosis of 'at risk' of specific NDDs (i) CP, (ii) ASD, (iii) FASD, and/or (iv) adverse NDO (non-specific) or (v) typically developing/borderline at 12 months CA compared to normative data.	
H2a	Indigenous infants at high risk of CP at 12 months CA will score HINE<70 (GMFCS I-III), or ≤40 (GMFCS IV-V); BSID-III >2SD below the mean (50% cognitive scale, 25% communication scale), PDMS-2 >1 SD below the mean (GMFCS I- III) or >2 SD below the mean (GMFCS IV-V) and PEDI-CAT >1SD below the mean (GMFCS I-III) or >2 SD below the mean (GMFCS IV-V) (mobility scale).
H2b	Indigenous infants with ASD symptomology at 12 months CA will have a greater number of risk markers on the AOSI and/or will score HINE <70, on average score >1 SD below the mean on the BSID-III (communication scale, cognitive scale), and PDMS-2, PEDI-CAT >2 SD below the mean (personal/social scale), ITSEA ≥1.5 SD below the mean (competence domain) and/or ≥1.5 SD above the mean (externalising, internalising, dysregulation domains).
H2c	Indigenous infants with FASD symptomology at 12 months CA will have microcephaly, ≤3 sentinel facial features and significant impairment (≥2 SD below the mean or equivalent) on ≥3 developmental domains including motor (PDMS-2 total motor quotient, PEDI-CAT mobility), neurological (<70 on the HINE), cognitive (BSID-III cognitive subscale, PEDI-CAT daily activities), communication (BSID-III language composite score), Adaptive behaviour/social skills (PEDI-CAT personal/social scales, ITSEA subdomains).
H2d	Indigenous infants at risk of adverse NDOs (non-specific) at 12 months will have significant impairment (>2 SD below the mean) on 1 domain and/or or mild to moderate impairment (>1SD below mean) in ≥2 domains including motor (PDMS-2 total motor quotient, PEDI-CAT mobility), neurological (<70 on the HINE), cognitive (BSID-III cognitive subscale, PEDI-CAT daily activities), communication (BSID-III language composite score), Adaptive behaviour/social skills (PEDI-CAT personal/social scales, ITSEA).
H2e	Indigenous infants typically developing (≤1SD below the mean or equivalent on all developmental domains) or borderline (mild delay; between 1 and 2SD below the mean on 1 domain) at 12 months CA will score >70 on the HINE (neurological), and ≤1 SD below the mean on the PDMS-2, BSID-III, PEDI-CAT and ITSEA (motor, cognition, communication, self-care and personal/social scales, behaviour).
AIM 3 To determine the clinimetric properties of outcome and/or predictive measures used to assess a cohort of 'at risk' Indigenous infants (GMA, HINE, RNDA, ASQ-TRAK, BSID-III, PDMS-2, PEDI-CAT, ITSEA) in terms of (i) construct validity, (ii) reliability, (iii) cultural acceptability and (iv) clinical utility/feasibility.	

H3a	Indigenous infants who are assessed to have ≥2 neurodevelopmental impairments (NDI) and/or score moderate to severe impairment on any domain of the RNDA at 6 months and 12 months CA will have suboptimal HINE scores at 6 (<65) and 12 (<70) months CA.
H3b	Indigenous infants who score 'at risk' on the communication (<16) and/or problem-solving (<28) domains of the ASQ-TRAK at 12 months CA will score ≥2SD below the mean on the language and/or cognitive domains of the BSID-III at 12 months CA.
H3c	Indigenous infants who score 'at risk' on the gross motor (<22) and/or fine motor (<35) domains of the ASQ-TRAK at 12 months CA will score ≥2SD below the mean on the Gross Motor and/or Fine Motor Quotients of the PDMS-2 at 12 months CA.
H3d	Indigenous infants who score 'at risk' on the personal-social (<22) domain of the ASQ-TRAK at 12 months CA will score ≥2SD below the mean on the corresponding domain of the PEDI-CAT and ITSEA at 12 months CA.
H3e	There will be strong interrater reliability and agreement (k>0.8) between clinicians and community health workers for the HINE, RNDA and ASQ-TRAK.
H3f	The clinical utility and cultural acceptability of screening tools used to predict later neurodevelopmental outcomes of Indigenous infants at ≤9 months (GMA, HINE, RNDA and ASQ-TRAK) will be higher than that of tools used to measure developmental outcomes at 12 months CA (PDMS-2, BSID-III, PEDI-CAT, ITSEA).
AIM 4 To determine the relationship between (i) perinatal variables, (ii) maternal risk factors and outcomes of (i) motor, (ii) cognition and (iii) development for Indigenous infants at 12 months CA.	
H4a	Adverse perinatal variables including, gestational age (<37weeks) , low birthweight (<2500g), events that signify complications during labour and delivery, adverse neonatal medical complications, and post-neonatal events including, infection, non-accidental injury, cerebro-vascular accident, will be significantly associated with lower scores on neurological, motor, cognitive, developmental and behavioural assessments at 12 months CA (HINE, PDMS-2, BSID-III, ASQ-TRAK, PEDI-CAT, RNDA, ITSEA).
H4b	Maternal risk factors (significant maternal medical conditions, antenatal medical complications and treatment, antenatal substance use and social risk factors as determined by the Social Risk Index), will be associated with lower scores on neurological, motor, cognitive, developmental and behavioural assessments at 12 months CA (HINE, PDMS-2, BSID-III, ASQ-TRAK, PEDI-CAT, RNDA, ITSEA).
H4c	Elevated caregiver stress, anxiety and depression on the DASS-21 will be associated with lower scores on neurological, motor, cognitive, developmental and behavioural measures in Indigenous infants at 12 months CA (HINE, PDMS-2, BSID-III, ASQ-TRAK PEDI-CAT, RNDA, ITSEA).

METHODS

Study Design

This multi-site prospective cohort study of 120 Indigenous infants will be conducted in Queensland, Australia. The methodological design follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines[101].

Participants

A cohort of 120 Indigenous infants with identified risk factors for adverse NDOs will be recruited. Recruitment will occur over an 18-month period (birth years 2020-2022) from the Neonatal Intensive Care Unit (NICU), Special Care Nurseries (SCN), Paediatric wards and outpatient clinics across Queensland.

Inclusion Criteria

Infants eligible for screening will be those aged 0-9 months CA with one or both biological parents identifying as Aboriginal and/or Torres Strait Islander, who meet the following criteria:

(i) pregnancy complications, LBW (<2500g), born preterm (<37 weeks gestation), or at term with Hypoxic Ischemic Encephalopathy (HIE), 5 min Apgar <6, history of neurological risk factors (e.g., admission to NICU/SCN, congenital abnormalities, SGA, seizures), post-neonatal complications (e.g., head injury, stroke, infection, non-accidental injury) or maternal risk factors that may impact neonatal outcomes (e.g. medical conditions, family history of adverse NDOs, antenatal substance use).

(ii) reside in Queensland.

Exclusion Criteria

Infants with major congenital or chromosomal abnormalities identified as part of routine medical care.

Recruitment procedures

Infants will be recruited through Queensland Hospital and Health services (HHS) and Aboriginal Community Controlled Health Organisations with ethics and governance approvals in place (see acknowledgments). The study will be introduced to parents or caregivers of infants who meet eligibility criteria by an Indigenous Liaison Officer (ILO) or member of staff from the recruiting sites. If families are interested in participating and consent to being contacted, a member of the research team will contact the family and provide information regarding the study, including a culturally adapted parent information statement. The research team member, who is not associated with the infant's care, will explain the study in more detail and answer all parent questions prior to seeking informed consent for study participation. Families will be given the option to verbally discuss the parent information sheet with an ILO or Indigenous Community Health Worker (CHW) prior to providing written informed consent to participate. Once signed consent is obtained, the infant will be enrolled in the study and will commence the relevant screening assessments.

Sample Size

This study aims to predict a later diagnosis of (i) typical development or 'at risk' of specific NDD, (ii) CP, (iii) ASD, (iv) FASD and/or (v) adverse NDO (non-specific) in a population of Indigenous infants with known exposure to early life risk factors. The projected sample size of 120 Indigenous infants is based on the expected number of new diagnoses of CP, ASD, FASD or adverse NDOs over an 18-month period at the study sites. The Cairns and Townsville hospitals have a potential combined total of 1400 infants admitted to their NICU and SCN's per year. Approximately 38 percent (n=540) of these infants have one or both biological parents who identify as Indigenous. The proportion of participating children with an adverse NDO we are likely to observe in the LEAP-CP cohort has been estimated by combining data from Australian data registers with data from a retrospective audit of a cohort of high risk infants admitted to the Townsville Hospital NICU or SCN during 2019-2020.

The Western Australia Cerebral Palsy register is the register that has reported rates of CP in Indigenous children for the longest duration and has a current estimate of 4.01 CP cases per

1000 births. Incidence of ASD in Indigenous Australian children is hypothesised to be approximately equal non-Indigenous rates, at between 7 and 15 ASD cases per 1000 births[6,81]. Incidence of FASD in Indigenous Australians is estimated at 17 FASD cases per 1000[102], but could be as much as 10-times higher in some remote communities[98]. The overall number of Indigenous children who have either developmental delay or an adverse NDO may range from 10% in low risk cohorts[14] to 30% in high risk remote communities[10].

A retrospective audit of high-risk Indigenous children admitted to the Townsville Hospital neonatal unit or SCN identified 16 children with known outcomes at 12 - 24 months CA. Of these children, 25 percent were at high risk of CP, 25 percent were at risk of a non-CP NDO, 31 percent had a non-neuromotor delay while 19 percent had no neurodevelopmental concerns. Overall >80 percent of these children were classed as having at least mild delay, although it should be noted that these children were at higher risk for an NDO than those who will participate in the LEAP-CP cohort. For the 120 children recruited to the LEAP-CP cohort we estimate approximately one-third (33 percent) will be identified as being at risk of an NDO. This will allow us to estimate the diagnostic accuracy of tools to within ± 12% (sensitivity) and ± 9% (specificity), assuming accuracy of 80 percent. When identifying characteristics associated with an NDO, assuming we have a binary predictor variable with equal numbers in each category and a baseline risk of 0.33, we will have 80 percent power (alpha=0.05) to identify relative risks of 1.75 or greater.

Engagement with the Aboriginal and Torres Strait Islander Community

Members of key Indigenous communities across Queensland will be actively engaged at all stages of the research program. Consultation regarding design, cultural adaptation and delivery of information has been and will continue to be sought throughout program delivery, final analysis and data interpretation. Strategies targeting key components of cultural safety and sensitivity, consultation and co-design, capacity building and sustainability, are fundamental to the cultural framework that underpins this study and will be led by Indigenous co-investigators. Consumer engagement will be embedded into the study at key screening and outcome timepoints to evaluate parent/caregiver and CHW experience and satisfaction with the screening process and appropriateness and feasibility of assessments.

Data Collection Methods

Data collection will commence following consent and enrolment. Extensive perinatal data will be collected from the infant's medical records, including gestational age, birthweight, sex, birth history, neonatal course and maternal risk factors (See S1: LEAP-CP Medical Checklist: Part 1 – Perinatal data and birth history). Primary caregivers will complete a baseline parent questionnaire that collects detailed socio-demographic information including, maternal and paternal education and employment, social support, family structure and prenatal exposures (See S1: LEAP-CP Medical Checklist: Part 2- Socio-demographic Information). Caregivers will be given the option to complete this form either independently or during a supported interview with an ILO or Indigenous CHW.

Participants will be screened at two time points, (i) birth to 5 months CA, and (ii) 4 to 9 months CA. Infants can enter the study at any time between birth and 9 months CA, and will commence

the relevant screening protocol based on their age at study entry. Outcome measures will be completed at 12 months CA (See Figure 1: LEAP-CP prospective cohort study timeline).

Birth to 5 months CA (Screening stage 1)

Infants recruited prior to 9 weeks CA, will be assessed as an inpatient or outpatient, using the General Movements Assessment, (GMA, writhing period)[48]. The assessment will be recorded by a member of staff who is trained in the procedural guidelines for GMA and uploaded to a secure server. Between 12- and 17-weeks CA infants will be assessed twice using the GMA (fidgety period) via video taken at a clinic appointment or by an application on the caregiver's phone and later uploaded to a secure server. The General Movements smartphone application (Baby Moves;[103]) will be set up on the caregiver's phone by a member of hospital staff or the research team on recruitment to the study. Culturally adapted written/pictorial instructions will be provided to guide caregivers how to video their infant's movements, with support offered by an ILO/CHW. A reminder will be sent via the Baby Moves app to caregivers to ensure videos are recorded at two time-points (ideally at 12- and 14-weeks CA). All GMA videos will be viewed and scored by a minimum of two assessors who are advanced trained by the General Movement Trust and are masked to the participant's identity and medical history. The General Movements Motor Optimality Score (MOS) will be assessed and scored simultaneously using the infant's fidgety GMA videos by the same independent assessors[104].

Assessments at 4 to 9 months CA (Screening stage 2)

The second stage of screening will occur from 4 to 9 months CA. Infants will attend an appointment with a local health care worker where they will be assessed using the HINE, Rapid Neurodevelopmental Assessment (RNDA), Ages and Stages – Aboriginal adaptation (ASQ-TRAK) and clinical assessment of physical features of FASD (photograph with or without direct measurement). The mother or primary caregiver will complete the Depression Anxiety Stress Scale (DASS-21). Developmental assessments will be administered and scored live by a trained allied health professional, paediatrician, CHW or child health nurse and will be video recorded to allow for independent scoring by a masked assessor. Results from all early screening assessments will be provided to the infant's treating team with parental/caregiver consent. Infants who are rated absent or abnormal fidgety movements on the GMA at 3 months CA and/ or receive a suboptimal HINE score at 4-9 months CA are considered to be at 'high risk' of CP and /or adverse NDO and will be referred to the LEAP-CP intervention trial and linked with local community health services.

Outcomes at 12 months CA

At 12 months CA (± 1 month) all participants will attend an appointment at their local health service. Infants will be assessed by a trained allied health clinician on the HINE, RNDA, ASQ-TRAK, Peabody Developmental Motor Scales – 2nd Edition (PDMS-2), and the cognitive and language scales of the Bayley Scales of Infant Development – 3rd edition (BSID-III). Infants will complete diagnostic specific outcome measures (i) Autism Observation Scale for Infants (AOSI; ASD) and (ii) clinical assessment of physical features of FASD (photograph with or without direct measurement) to determine the presence of symptomology and risk of a later diagnosis of ASD and/or FASD. Assessments will be recorded to allow independent scoring

by an assessor masked to the infant's risk of adverse NDOs, medical history and previous assessment findings. A paediatrician, masked to the infant's developmental history, will complete the medical assessment for differential diagnosis from video and photographic (FASD symptomology) assessment (See S2: LEAP CP: 12-month Medical Assessment – Differential Diagnosis). Caregivers will complete the DASS-21, Infant Toddler Social-Emotional Assessment (ITSEA), Pediatric Evaluation of Disability Inventory - Computer Adaptive Test (PEDI-CAT) and health resource and information questionnaire, either independently or as an interview supported by an ILO or CHW (See S3: LEAP – CP Medical and Allied Health Resource Form). Child outcomes will be provided to parents/caregivers via written report and results will be forwarded to the infant's treating team with parental/caregiver consent.

MEASURES

Infant Predictor Variables

Prechtl's Qualitative Assessment of General Movements (GMA)

Prechtl's Qualitative Assessment of General Movements (GMA) is a predictive and discriminative tool used to longitudinally observe the quality of early spontaneous movement patterns in infants from birth to 20 weeks CA. The GMA demonstrates high diagnostic accuracy, 97 percent specific and 95-98 percent sensitive, at 3 months CA for detecting infants with a later diagnosis of CP[44-46]. General Movements (GMs) are assessed over specific time periods as either writhing (birth – 9 weeks CA) or fidgety (9-20 weeks CA). Writhing movements are rated as normal, characterised by complex, variable, fluent movements involving the whole body, or abnormal, classified as either poor repertoire, cramped synchronised or chaotic[47,48]. Fidgety movements (FMs) are present from 9 weeks until voluntary, more purposeful movements become predominant[47,48]. Typical (normal) FMs are defined as small amplitude, multidirectional movements, of the trunk, neck and limbs, of moderate speed, that are continuous in the awake infant, except during periods of crying, fussing and focussed attention[47]. Atypical FMs are classified as either absent or abnormal, referring to either the absence (absent) or exaggeration (abnormal) of typical fidgety movements[47]. While the absence of FMs at 3 months is the best predictor of CP[45], abnormal GMA at writhing age has been associated with later cognitive delays[105], and abnormal fidgety GMA (abnormal or absent) has been associated with early motor delay related to prenatal substance use[36], and is emerging as a potential marker of atypical movement patterns in infants later diagnosed with ASD[35,106]. Assessment of the GMA requires a 3-5-minute video of the infant lying in supine, during periods of active wakefulness, free from distractions. In this study fidgety GMA will occur at two timepoints (ideally between 12- and 17-weeks CA) to give optimal opportunity for FMs to emerge within the 'peak' window[107] and will be scored by at least two advanced trained assessors, masked to the infant's medical and clinical history, to decrease the potential impact of measurement bias.

General Movements Motor Optimality Score (MOS)

The MOS is a more detailed analysis of an infant's fidgety GMA to determine their concurrent motor repertoire at 3-5 months CA by observing postural patterns and movement quality, across five subcategories[104]. The score of each subcategory; quality of fidgety movements, quality of movement patterns, age-adequate movement repertoire, postural patterns and movement character, combine to give a total MOS ranging from 5 to 28[104]. Scores ≥25 are optimal and indicative of typical outcomes, scores ranging from 20 to 24 are mildly reduced and MOS <20 requires intervention[57,104]. The presence of specific movement patterns and low scores on the MOS are predictive of a later CP diagnosis and may provide early markers for CP severity, subtype and topography[104,108,109]. Increasing evidence supports the MOS as a prognostic indicator for adverse NDOs (non-CP), and therefore, its function as a transdiagnostic screening tool. Suboptimal MOS scores have been associated with later outcomes of minor neurological dysfunction, language impairments, learning and behavioural difficulties in children without a CP diagnosis[110,111]. Additionally, a monotonous movement character was identified in almost 60% of infants who were prenatally exposed to alcohol and addictive substances[36], has been found in infants with later diagnoses of NDDs (non-CP) including ASD[51] and genetic disorders[104], and, has been linked to cognitive delays at school age in a cohort of high risk infants[112]. The MOS will be assessed and scored concurrently with fidgety GMA, by the same masked, advanced trained assessors.

Hammersmith Infant Neurological Evaluation (HINE)

The HINE is a quantifiable, neurological examination for infants aged 2-24 months CA[113]. It is predictive of suboptimal neurodevelopmental outcomes with 90 percent accuracy in predicting CP in infants aged >18 weeks CA.[44,114]. The HINE is divided into 3 sections, section 1 consists of 26 items that assesses infant neurological function across five domains: cranial nerves, posture, tone, reflexes and movements. Sections 2 and 3 evaluate the infant's motor development and state of behaviour, these sections are not scored[113]. Each item from section 1 is scored from zero to three, where a score of three is indicative of an optimal item response. Item scores are combined to determine a global optimality score, with a maximum possible score of 78. An infant's global score is compared to age specific optimality scores and cut-offs to determine risk of adverse NDOs[113]. Suboptimal HINE scores (<65, <70) at 6 and 9-12 months respectively are associated with significant delays and/or CP at 2 years[37], with further age specific cut-points (<57 , <60, <63 and <66) at 3, 6, 9 and 12 months respectively, predictive of a later diagnosis of CP[54]. Infants with hemiplegic CP or milder neurological disorders may score above age-specific cut offs[52,54]. Differences observed in item responses between the left and right sides are recorded as asymmetries and are combined to obtain a total asymmetry score. A total of ≥ 5 asymmetries are associated with increased risk of unilateral CP[52]. The HINE is accessible, quick to administer, approximately 5-10 minutes, and has good interobserver reliability, even when performed by less experienced staff[113].

Rapid Neurodevelopmental Assessment (RNDA)

The RNDA is a criterion-based instrument, originally designed to comprehensively assess and identify children 'at risk' of neurodevelopmental impairment (NDI) living in low to middle

income countries with limited access to health screening services[80]. The screening tool is intended for use by lay health workers and has been successfully integrated into Aboriginal Health clinics at Gidgee Healing in Mt Isa, Queensland[115,116]. The instrument assesses the functional status of children aged 0-9 years to determine the presence and severity of NDIs across multiple domains[80,117,118]. Infants aged 1-24 months CA are assessed across eight domains: gross motor, fine motor, vision, hearing, speech, cognition, behaviour and seizures. Each item is scored on a 4-point scale, as normal = 0, mild= 0.5, moderate=1 or severe=2 impairment. The sum of item scores are used to determine the presence and degree of impairment for each domain[119]. The RNDA has been validated in infants ≤2 years CA to determine the presence of NDI vs no NDI[80] and demonstrates moderate to high agreement with the Bayley Scales of Infant Development – second edition and BSID-III for identifying infants aged <12 months CA with and without NDIs[80,120]. The RNDA has good face validity, evident in its acceptability by caregivers, clinicians and infants, and has been culturally adapted for use in other countries[80,120]. The RNDA has high interrater reliability among medical professionals across the domains of gross motor (k=1.00), behaviour (k=1.00), fine motor (k=0.93) and seizures (k=0.91), with moderate agreement for cognition (k=0.80), hearing (k=0.78) and speech (0.63)[80]. A similar level of agreement was also demonstrated between local community workers and trained health professionals across cognition, speech, behaviour, gross and fine motor domains[120]. Administration time for the RNDA is between 30-45 minutes and must be completed by a trained clinician or health worker[80].

Ages and Stages Questionnaire, Australian Aboriginal adaptation (ASQ- TRAK)

The ASQ-TRAK (adapted from the Ages and Stages Questionnaire 3rd edition;[79]) is the only developmental screening tool that has been adapted and validated specifically for use in an Australian Indigenous context[121,122]. The ASQ-TRAK demonstrates acceptable accuracy, sensitivity (71 percent), specificity (92 percent), for detecting developmental concerns in Indigenous children, and, has demonstrated concurrent validity with the BSID-III, with moderate correlation between corresponding domain scores on both tools[121]. The ASQ-TRAK consists of interview-based questionnaires available for children aged 2, 6, 12, 18, 24, 36 and 48 months, assessing outcomes across five areas; communication, gross motor, fine motor, problem solving, personal-social[123]. The screening tool contains the same items and scoring as the ASQ-3 but is based on a caregiver interview, with opportunity for the child to demonstrate skills. Culturally relevant adaptations to the ASQ-3 include, translation into local language and item modifications to ensure cultural relevance[123]. Individual items are assessed as “yes”, “sometimes” or “not yet” to ascertain a score of 10, 5 or 0 respectively. Individual, domain specific, item scores are combined to determine the total domain score (maximum = 60). Scores are compared to domain specific cut-offs to determine risk of developmental delay, with further assessment recommended for infants who score below the cut off, or ‘at risk’, for any domain[122]. The ASQ-TRAK has proven face validity and was determined to be culturally relevant and acceptable by Aboriginal health care workers and parents[123,124]. The screener takes 30-60 minutes to complete and can be administered by trained health care workers[121].

Outcome Measures

1. Infant

Outcomes will be assessed at 12 months CA (± 2 weeks) by a trained allied health clinician and videoed for scoring by a researcher masked to perinatal data and earlier assessment data points.

Peabody Developmental Motor Scales second edition (PDMS-2)

Infant primary motor outcomes at 12 months CA will be assessed using the PDMS-2, a standardised, norm-referenced measure used to evaluate the gross and fine motor development of children aged birth to 6 years[125]. The gross motor component is comprised of four subtests: reflexes, stationary, locomotion and object manipulation. Two subtests, grasping and visual-motor integration, form the fine motor component[125]. Individual items are allocated a score from zero to two based on performance, 0 (unable to perform), 1 (partial performance) or 2 (correct performance). Subtest raw scores are used to determine motor outcomes and ascertain the presence and severity of motor delay. The PDMS-2 has demonstrated predictive validity, sensitivity (92 percent), to identify abnormal development at 18 months in preterm infants assessed at 8 months[126]. The assessment has concurrent validity with both the BSID-III[127] and the Gross Motor Functional Measure[128]. The PDMS-2 is responsive to change in a population of infants[129] and toddlers with CP[130]. The assessment takes 45-60 minutes to complete, with formal training not required for the administration and scoring of the PDMS-2.

Bayley Scales of Infant Development – 3rd edition (BSID-III)

The BSID-III is the gold standard, norm-referenced assessment for measuring the development of infants and toddlers, aged 1–42 months, to determine infant cognitive and communication outcomes at 12 months CA. The BSID-III comprises five scales, cognitive, language, motor, social-emotional and adaptive behaviour. Items are administered in a standardised procedure and scored as either credit=1 or no credit=0. A composite score of >2 SD below the mean on any scale is indicative of delay and supports the need for intervention[131]. In this study we will use the BSID-III cognitive and language scales to assess infant outcomes at 12 months CA. The BSID-III (cognitive and language scales) have demonstrated predictive validity for outcomes on the Weschler Preschool and Primary Scale of Intelligence –III at 4 years of age[132]. Internal consistency reliability and test re-test reliability were determined for the composite and subtest scores on the Bayley III cognitive and language scales across all ages, with higher reliability demonstrated in age groups >6 months of age[131]. The BSID-III low motor/low vision version will be used to improve validity when assessing children with mild to moderate motor and/or vision impairment[133]. While the Bayley IV is now available[134] the Bayley III will be used in this study to compare this Indigenous cohort to other non-Indigenous Australian cohorts[135]. A trained professional is required to administer the assessment, average time taken to complete varies with age and ranges from approximately 50 – 90mins[131,136].

The Pediatric Evaluation of Disability Inventory-computer adaptive test (PEDI-CAT):

Developmental outcomes in self-care, mobility and social function will be assessed at 12 months CA using the PEDI-CAT, a standardised, norm-referenced assessment of independence in self-care[137]. The PEDI-CAT has been designed for use from birth to 21 years of age and has been Rasch analysed in children with disability and typical development[137]. The instrument measures functional outcomes across four domains, daily activities, the ability to perform living skills, mobility, the ability to move around the home and in the community, and, social/cognitive the ability to participate and effectively engage in social situations. Responsibility, the fourth domain, will not be assessed in this study[137]. The tool is administered via a web-based application (Q-global), allowing parents/caregivers to self-report their child's independence on each domain. The PEDI-CAT uses an item bank which automatically lowers the number of test items dependent on how the child is scoring[137,138]. Items are scored on a 4-point difficulty scale with responses ranging from unable to easy. Normative scores are reported as a T-score and an age percentile range ($<5^{th}$, $5^{th} – 25^{th}$). The PEDI-CAT has good discriminant validity in CP populations, between children with and without disability, and, demonstrates concurrent validity with the Wee-FIM in children with brain injury and developmental disabilities[139-141]. The PEDI-CAT is frequently used as an assessment to determine entry and allocation of resources for children entering the Australian National Disability Insurance Scheme (NDIS)[142]. The test is valid, reliable and responsive in this population, takes 10-15 minutes to complete, and test administration requires no formal training[141,143].

Infant Toddler Social and Emotional Assessment (ITSEA)

The ITSEA is a 168 item, parent-report questionnaire designed to evaluate social-emotional and behavioural competencies and difficulties in infants aged 12 months to 3 years old[144]. The instrument measures items across four behavioural domains; externalising, internalising, dysregulation and competencies. Items are scored on a 3-point (0-2) scale, not true/rarely (0), somewhat true/sometimes (1), and, very true often (2)[144]. The ITESA is discriminative between high and low risk infants with social-emotional difficulties at 12 months of age[145], and demonstrates strong test-re test reliability (α=.75-.91)[146].

2. Diagnostic assessments

At 12 months CA infants will be assessed by a paediatrician who will complete a medical assessment for differential diagnosis (S2: LEAP-CP 12-month Medical Assessment) including documenting the presence of ASD and FASD symptomology. Functional severity, motor type and distribution of CP will be ascertained for infants who have a confirmed or high-risk diagnosis of CP.

Diagnosis of Cerebral Palsy

Confirmed or high risk CP will be diagnosed according to published guidelines[147-149], based on clinical history (LEAP-CP Medical checklist) and videoed HINE and PDMS-2 assessments.

Motor type and distribution

Motor type will be classified as spastic, dystonic, ataxic, choreoathetosis, mixed CP or unclassifiable according to Surveillance of Cerebral Palsy in Europe (SPCE) guidelines [148]. Motor distribution will be classified by number of limbs impaired and uni- or bi-lateral distribution by an independent assessor.

Functional severity

The Gross Motor Functional Classification System (GMFCS) has validity, reliability and stability for the classification and prediction of motor function of children with CP aged 2-12 years[150-152]. The GMFCS extended and revised version, 0-2 year descriptors, will be used to classify the gross motor abilities of infants at 12 months CA[153]. The GMFCS has been correlated with CP motor type and distribution[154].

The Mini Manual Abilities Classification Scale (MACS) is used to classify hand function and abilities in children aged 0-4 years and is the gold standard for classifying infant's ability to handle objects in daily activities[155]. An independent assessor will use videos to observe and classify children in one of five functional categories for each scale.

ASD symptomology

The Autism Observation Scale for Infants (AOSI) will be used to measure ASD symptomology at 12 months CA [156]. The AOSI, a semi-structured observational tool, was designed to assess the presence and emergence of specific ASD related behaviours in infants aged 6-18 months[71,156]. The experimenter led tool assesses 18 items, individual item scores range from 0-3 and are combined to obtain a total score, with higher scores indicating elevated risk of ASD behaviours[71]. The presence of 7 or more risk markers at 12 months was 52% sensitive and 74% specific for an ASD diagnosis at 3 years[75]. The AOSI differentiates between high-risk and low-risk infants at 12-18 months[73,75,76,157]. Inter-rater reliability for individual items and total scores is excellent (0.92 and 0.93, respectively) at 12 months and test -retest reliability is acceptable[71].

FASD symptomology

Assessment of PAE

The Alcohol Use Disorders Identification Test- Consumption (AUDIT-C) will be used to ascertain the potential level of fetal risk associated with maternal alcohol use during pregnancy (pre- and post-pregnancy recognition). The validated, sex-specific version of the instrument comprises three questions as a standardised method of assessing maternal alcohol consumption [158,159]. An AUDIT-C score of ≥5 or a reported consumption of 5 or more standard drinks on one occasion is associated with increased risk of FASD[88,159].

Sentinel Facial features

Clinical assessment of facial features will be completed via direct measurement (where possible) and/or assessed from a photograph, analysed using the University of Washington facial analysis software[160]. Smooth philtrum and thin upper lip will be assessed using the University of Washington Caucasian or African American (depending on what is individually appropriate) lip-philtrum guide (1 or 2), where a rank of 4 or 5 meets criteria for FASD sentinel facial features. The Scandinavian (Stromland) chart will be utilised to measure palpebral fissure length where a result of ≥2 SD below the mean (<3rd percentile) is significant [88,161].

Standard frontal and oblique facial photographs will be analysed using the FAS Facial Photographic Analysis Software for facial dysmorphology assessment[160].

Severe Neurodevelopmental Impairment

Assessment of impairment will target five of the ten neurodevelopmental domains that reflect known areas of brain function affected by PAE[88]. Infant's neurological, motor, cognitive, language and adaptive and social skills will be assessed using standardized outcome measures at 12 months CA. Severe impairment will be defined as score of ≥2 SD below the mean, or equivalent, on the HINE (neurological), PDMS-2 (motor), Bayley III (cognitive and language scales), PEDI-CAT (adaptive/social) and ITSEA (behaviour)[88]. Infants with a head circumference less than <3rd centile and/or abnormal brain imaging including structural brain abnormalities will also be considered as criteria for severe brain structure/neurological impairment[88]. Presence and severity of impairment will be determined by assessors blinded to the infant's clinical history and predictor assessment outcomes.

Special considerations for infants

In children under 6 years of age with all 3 sentinel facial features and microcephaly a diagnosis of FASD with 3 Sentinel Facial Features can be made, regardless of confirmed PAE and in the absence of severe neurodevelopment impairment in 3 domains. In the absence of microcephaly, children under 6 years of age with all 3 sentinel facial features are considered 'at risk of FASD', whether PAE is confirmed or unknown[88].

3. Parent/Caregiver

Depression Anxiety Stress Scale (DASS-21)

Parent or primary caregiver mental health status will be assessed at two time-points (screening stage 2 and infant 12 month outcomes) using the DASS-21, a 21-item, self-reported tool designed to measure the presence of the negative emotional states of depression, anxiety and stress[162]. Individual items assess the presence of symptoms across 3 subscales (depression, anxiety and stress). Participants use a 4-point scale to reflect and rate the extent to which they have experienced each symptom over the past week. Item scores are combined to determine the severity; normal, mild, moderate, severe or extremely severe, for each emotional state[162]. The DASS-21 has demonstrated concurrent validity with the Beck depression and anxiety inventories[163,164] and has been utilised in a population of Indigenous mothers to assess maternal emotional wellbeing[165].

Co-Variates and Descriptive measures

Perinatal Data

An extensive record of antenatal, birth history and the neonatal course will be collected at the time of infant enrolment from medical records (See S1: LEAP-CP Medical checklist). Data collected will include:

i. Demographic data including gestational age, birth weight, sex and multiple birth status.
ii. Perinatal events that signify complications during labour and delivery, indicating increased risk of adverse NDO.

iii. Neonatal medical complications associated with adverse NDOs including early brain injury, infection, necrotising enterocolitis, respiratory distress, bronchopulmonary dysplasia, postnatal infant steroid therapy, neonatal surgery, retinopathy of prematurity, prolonged use of oxygen and feeding status at discharge.

iv. Maternal risk factors that may impact neonatal outcomes, including, antenatal medical complications and treatment, medical conditions (diabetes mellitus, epilepsy), antenatal substance use, mental health status and family history of adverse NDOs.

Clinical neuroimaging

Cranial Ultrasound (CUS) and MRI assessment findings will be collected and retrieved from Hospital records. Abnormal MRI, including white matter injury, cortical and grey matter lesions and brain maldevelopments may be indicative of neuroanatomy abnormalities predictive of adverse NDOs[45]. MRI findings will be utilised in the diagnostic process for CP and symptomology of FASD.

Demographic data

Demographic data will be collected at two time points:

The LEAP-CP Medical Checklist: Part 2 (S1), completed at study enrolment, details information regarding family structure and supports, primary language spoken at home, maternal and paternal education and employment status. The Social Risk Index (SRI) and the AUDIT-C questionnaire will be embedded into this document to ascertain level of family social risk and infant PAE[159,166].

The LEAP-CP Medical Resource form (S3), completed at or prior to the 12-month CA appointment, to provide information regarding their child's development, access to services and eligibility and/or access to NDIS funding.

Social Risk Index (SRI)

The 12-point SRI measures six aspects of social status; family structure, language spoken at home, maternal age at birth and primary caregiver education, occupation and income. Risk items are scored from 0-2, with a lower score associated with lower risk. Overall family risk scores will be classified as lower (≤1) or higher social risk (>2) [167,168]

DATA MANAGEMENT AND ANALYSIS PLAN

All data will be entered into a REDcap database by ID number (re-identifiable). Data analysis will be carried out using Stata v16.0[169] statistical software package . Predictor and outcome variables will be identified as continuous, categorical or binary. Analysis will explore means, variability and distributions of continuous variables and the rate of occurrence and distribution of binary variables. Infants will be categorised at 12 months CA as at risk of specific NDD, (i) CP, (ii) ASD, (iii) FASD (as defined by the presence of disorder specific symptomology) and/or (iv) adverse NDO (non-specific, defined as >2SD below the mean or equivalent on 1 developmental domain and/ or >1SD below mean in ≥2 domains), or (v) typically developing (≤1SD below the mean or equivalent on all developmental domains) or borderline (mild delay; between 1 and 2SD below the mean on 1 domain). Logistic regression analysis (binary outcomes), linear regression (continuous outcomes) and multinomial logistic regression (categorical outcomes) will be used to determine any associations between predictor and

outcome variables. Diagnostic statistics, including sensitivity, specificity, positive and negative predictive values and accuracy of the predictive assessments (GMA, MOS, HINE, RNDA and ASQ-TRAK) will be determined with 95% confidence intervals based on an outcome of 'at risk' of specific NDD, (i) CP, (ii) ASD, (iii) FASD and/or (iv) adverse NDO (non-specific) at 12 months CA. Perinatal variables, social and environmental data, caregiver mental health outcomes (DASS-21) and clinical neuroimaging will be utilised as descriptive measures and covariates in regression models.

DISCUSSION

Results of this study will inform service delivery of follow-up pathways for Indigenous infants at risk of adverse NDOs and their families. Our findings will inform culturally sensitive practice and enable clinicians to select both clinically meaningful and culturally appropriate tools to identify Indigenous infants at high risk of adverse NDOs at an earlier age. Early detection will fast track families to access early intervention services for Indigenous infants and families and enable early referral to the targeted motor and cognitive training in the LEAP-CP clinical trial (trial registration: ACTRN12619000969167) and or mainstream allied health services to promote optimal outcomes.

Strengths and Limitations

Infants will be recruited early to establish discharge pathways and a follow up plan, with local services. Engagement, and established connections with local health services will enable locally trained Indigenous CHWs to assist in the screening process for infants and families living remotely, with support provided via telehealth as required. Culturally adapted resources, developed in partnership with Indigenous co-investigators and consumers, will be utilised to facilitate safe and sensitive communication and practices throughout the screening and diagnostic process for infants and families. This study aims to foster local Indigenous workforce capacity through skill development and training opportunities and build upon current models of care to enable feasible and sustainable early detection programs for 'at risk' Indigenous infants. Assisting existing services to implement culturally appropriate screening programs will ensure these strategies and pathways can be embedded into regular service delivery models at the conclusion of the study.

The cultural, geographical and language barriers within this study present potential limitations and confounding factors. The ability to follow up Indigenous infants who live remotely may be a challenge, as remote locality is a reality for many QLD Indigenous communities, which limits ability to access health services. Infants who are identified as low risk following screening may be less likely to attend their 12-month CA follow up appointment, impacting study retention. In addition, challenges in recruitment and retention of health professionals in remote communities may further limit physical access to these services.

Ethics and Dissemination of findings

Ethics committee approvals were obtained from the appropriate Indigenous ethics/governance committees (see acknowledgements). There are no known health or safety risks associated with participation in any aspect of the described study. Cultural adaptations will be made to all resources and throughout the study families will be given the option to verbally discuss any

questions or concerns with an ILO or CHW to ensure comprehension of concepts, cultural and language barriers are addressed. Families can withdraw their child from the study at any time without explanation, without any penalty from staff at the treating or referring hospital or health service, or any effect on their child's care. Data collected in this study will be securely stored in a coded re-identifiable form (by ID number at the University of QLD). Summary data of outcome measures will be shared with the treating clinician and/or team with the parent/caregiver's permission.

Findings of this study will be of interest to medical, allied health and community health workers, working with Indigenous infants and families in urban, rural and remote communities. Findings will be disseminated via peer-reviewed publications, conference presentations, clinical practice guidelines outlining culturally appropriate screening tools and sensitively communicating a diagnosis and resources including culturally adapted factsheets.

ABBREVIATIONS

AOSI	Autism Observation Schedule in Infants
ASD	Autism Spectrum Disorder
ASQ-TRAK	Ages and Stages – Aboriginal adaptation
AUDIT-C	Alcohol Use Disorders Identification Test- Consumption
Baby Moves	General Movements smartphone application
BSID-III	Bayley Scales of Infant and Toddler Development – Third Edition
CA	Corrected age
CHW	Community Health Worker
CP	Cerebral Palsy
CUS	Cranial Ultrasound
DASS-21	Depression Anxiety Stress Scale
FASD	Fetal Alcohol Spectrum Disorder
GMA	General Movements Assessment
HHS	Hospital and Health services
HINE	Hammersmith Infant Neurological Examination
ILO	Indigenous Liaison Officer
ITSEA	Infant Toddler Social-Emotional Assessment
LBW	Low Birth Weight
MRI	Magnetic Resonance Imaging
NDD	Neurodevelopmental Disorder
NDO	Neurodevelopmental Outcome
NDI	Neurodevelopmental Impairment
NICU	Neonatal Intensive Care Unit
PAE	Prenatal Alcohol Exposure
PNN	Post neonatal
PDMS-2	Peabody Developmental Motor Scales – 2nd Edition
PEDI-CAT	Pediatric Evaluation of Disability Inventory - Computer Adaptive Test
RNDA	Rapid Neurodevelopmental Assessment
SCN	Special Care Nursery
SGA	Small for Gestational Age
SRI	Social Risk Index

COMPETING INTERESTS

The authors declare they have no competing interests.

AUTHOR'S CONTRIBUTIONS

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Associate investigators that have provided input into study design: MP,RF,LMc,MB,KP,AP, MK,PE,FG
Study personnel responsible for ethics applications and reporting: KB,CL,RB,LR
Study personnel responsible for writing the protocol manuscript: CL,RB,KB,NR,MB,RW,LR
Study personnel responsible for recruitment, data collection, analysis and implementation of the study: CL,KB,RB,MB,AB,LR.
Chief investigators that will take lead roles in publication of the clinical outcomes of the study: CL,RB,KB,MB,RW,AB,NR,LR.
All authors have read and approved the final manuscript

COLLABORATOR CONTRIBUTIONS

Collaborators who have provided assistance with patient care and data collection: Apunipima Cape York Health Council, Gidgee Healing, Gurriny Yealamucka Health Service Aboriginal Corporation, Townsville HHS, Cairns and Hinterland HHS, Children's Health Queensland HHS

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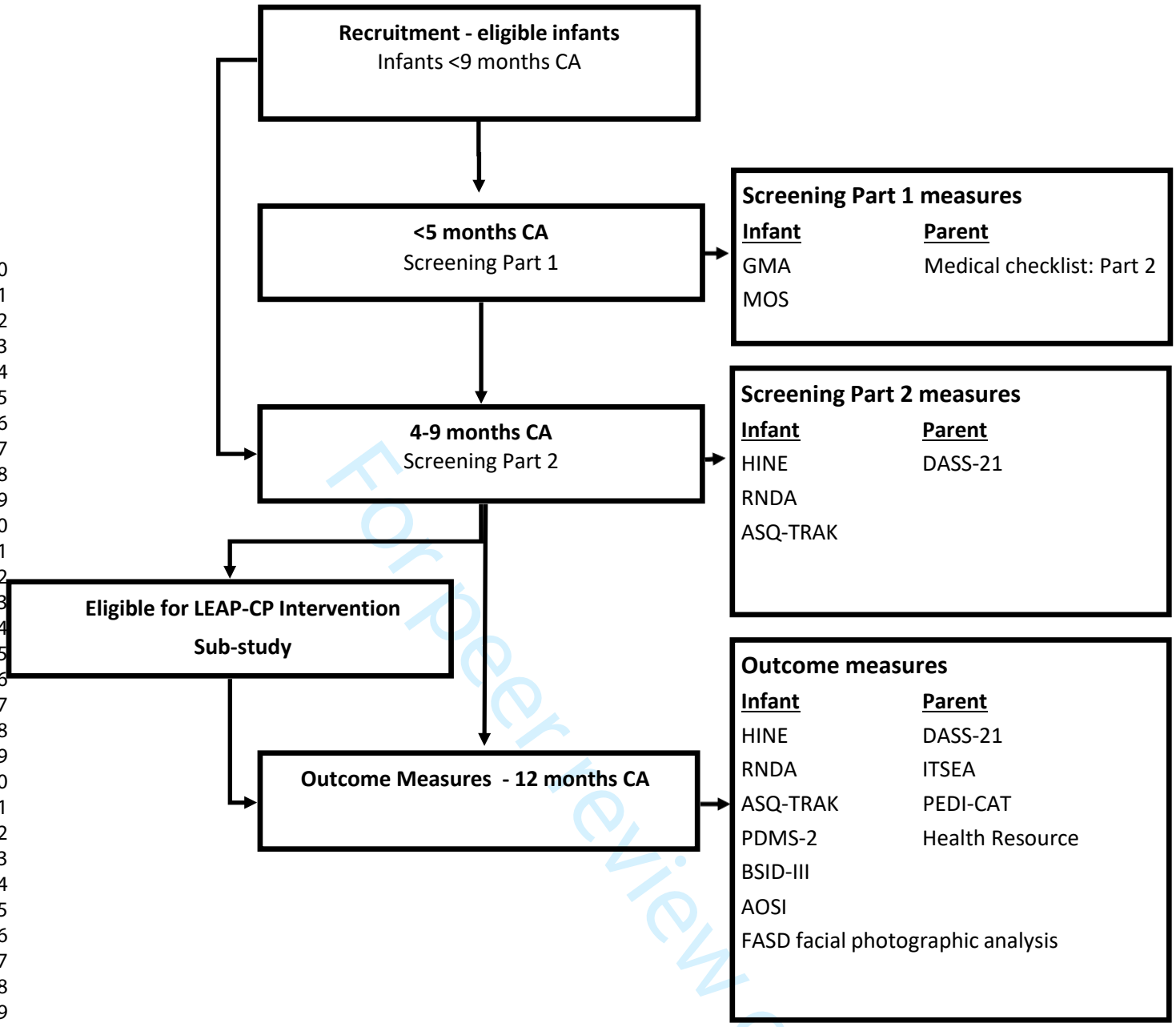

Figure 1: LEAP-CP prospective cohort study timeline

Key: GMA= Prechtl's General Movements Assessment, MOS= General Movements Assessment Motor Optimality Score, HINE= Hammersmith Infant Neurological Examination, RNDA= Rapid Neurodevelopmental Assessment, ASQ-TRAK= Ages and Stages Questionnaire-Aboriginal Adaptation, PMDS-2= Peabody Developmental Motor Scales 2nd Edition, BSID-III= Bayley Scales of Infant Development 3rd Edition, PEDI-CAT= Pediatric Evaluation of Disability Inventory - computer adaptive test, AOSI= Autism Observation Schedule in Infants, FASD facial photographic analysis, DASS-21= Depression Anxiety Stress Scale, ITSEA= Infant Toddler Social Emotional Assessment

Supplementary Information

S1: LEAP-CP Medical checklist: Part 1 and 2

Study ID: ☐☐☐ **Date:** ☐☐/☐☐/☐☐☐☐

Form completed by: **Interviewer initials:** ☐☐

Part 1: Perinatal data and Birth History – collected from Medical record

Infant details

Estimated date of delivery	
Date of birth	
Gestational age at birth (weeks.days)	
Maternal age at birth	
Gender	O Male O Female O Indeterminate
Multiple Births	O Singleton O Twin O Triplet O Surviving twin from multiple (eg singleton birth from triplet pregnancy, sibling died in utero or at birth)
Order of birth for multiples	
Birthweight (grams)	
Apgar at 1 minute	
Apgar at 5 minutes	
Resuscitation	O Nil (includes suction & O2 therapy) O Minor (bag and mask, CPAP or Hi-flow) O Major (intubation, CPR, adrenaline) O Resuscitation data not recorded

Infant complications

Respiratory (tick all that apply) Other respiratory issue please specify	O No (includes suppl O2 for <4 hrs) O Requiring ongoing ventilation or CPAP O Pneumothorax O Pneumonia O Other
Chronic lung disease (O2 and or ventilatory requirement at 36 weeks corrected age)	O Yes O No
Hypxoic Ischemic Encephalopathy (HIE)	O Yes O No
Sarnat stage or severity of HIE	O Stage 1 (mild) O Stage 2 (moderate) O Stage 3 (severe)
Received cooling	O Yes O No
Patent ductus arteriosus (PDA)	O No O Yes O Not documented
If yes to PDA, tick all that apply	O No treatment O Diuretics O Fluid restriction O Indomethacin/ibuprofen/paracetamol

	O Surgery
NEC	O No O Suspected (clinical signs, Xrays normal, nil by mouth &/antibiotics <5 days) O Definite (Xray changes, ≥5 days nil by mouth &/or triple antibiotics &/or surgery)
Seizures Aetiology if known	O Yes O No
Surgery	O Yes O No
Please specify what surgery (tick all that apply) Other surgery, please specify	O Bowel resection O Inguinal hernia repair O Tracheostomy O PDA ligation O Rickham's reservoir O VP shunt O other
Jaundice requiring exchange transfusion	O Yes O No
Major malformation or genetic syndrome Please specify	O Yes O No
Retinopathy of Prematurity (ROP)	O No O Yes, no intervention required O Yes, received laser therapy O Yes, received Avastin (brand name for Bevacizumab) O Not examined
Left eye: Max stage of ROP as recorded by ophthalmologist	
Right eye: Max stage of ROP as recorded by ophthalmologist	
Hearing Screen result Referred hearing result	O Pass O Referred for further examination O Not examined

Cranial and MRI findings Ultrasound findings (most severe reported)

IVH Maximum IVH grade Left Maximum IVH grade Right	O Yes O No
Cystic PVL	O Yes O No
Please specify any other abnormal neuroimaging findings	
Age at time of CUS/MRI	
Where was the CUS/MRI completed	

Discharge details

LOS in hospital (days) NICU SCN Transfered to other hospital	
Discharged home on Oxygen	O Yes O No
Was the infant receiving any tube feeding on discharge home?	O Yes O No

Developmental History

Complications since birth (please tick all that apply) Other, please specify	O CNS infection (eg meningitis/ encephalitis) O Head injury O Near drowning O Non-accidental injury O Tumour O CVA O Cerebral malformation O Other

Maternal details

Maternal age at delivery	
Mode of delivery	O Vaginal O Caesarean – in labour O Caesarean – not in labour O Not documented
Specify Caesarean section	O Elective O Emergency
Did the infant have foetal growth restriction?	O Yes O No
Did the mother have any of the following medical conditions during this pregnancy?	O None O Pre-eclampsia O Essential hypertension O Thrombophilia O Diabetes - specify O Epilepsy O Respiratory - specify O Renal disease - specify O Cardiac disease - specify O Pulmonary - specify O Red cell isoimmunisation O Autoimmune disease - specify O Psychiatric (diagnosed) - specify O Substance use - specify O Other
Diabetes (please specify)	O Gestational O Type 1 diabetes O Type 2 diabetes
Respiratory (please specify)	

Renal disease (please specify)	
Cardiac disease (please specify)	
Pulmonary (please specify)	
Autoimmune (please specify)	
Psychiatric (please specify)	
Substance use (please specify)	
Other (please specify)	
Antepartum haemorrhage (bleeding after 20 weeks gestation)? If Yes, specify at what gestation	O Yes O No
Did the mother receive corticosteroids (to enhance foetal lung maturation)?	O Yes O No O Not documented
Antenatal corticosteroids (number of completed courses; 2 doses = 1 course)	O None O Incomplete (1 dose only) O 1 course O 2 courses O 3 courses O Information not documented
Did the mother receive any intravenous magnesium sulphate	O No O Yes O Not documented
Duration of ruptured membranes	O N/A or no data available O <24 hours O ≥24 hours
Were antibiotics given?	O No O Yes O Not documented
Did any of the following intra &/or post-partum complications occur? Other, please specify	O None O Intra-partum fever (in mother) O Preterm labour O Meconium O Breech O Shoulder dystocia O Delayed cry (>5 minutes after birth) O Lethargy or seizures within 72 hours of birth O Cord around neck O Other
Antenatal care Number of visits	O Yes O No

Medications

During the last 6 months has your child had medications for…

1. Epilepsy	O Yes O No
A. Which medication	
Frequency (per day)	☐☐
Dosage (per day)	☐☐
Duration (length of treatment)	
Any adverse effects?	O Yes O No
B. Which medication	
Frequency (per day)	☐☐
Dosage (per day)	☐☐
Duration (length of treatment)	
Any adverse effects?	O Yes O No
C. Which medication	
Frequency (per day)	☐☐
Dosage (per day)	☐☐
Duration (length of treatment)	
Any adverse effects?	O Yes O No

2. Saliva control	O Yes O No
A. Which medication	
Frequency (per day)	☐☐
Dosage (per day)	☐☐
Duration (length of treatment)	
Any adverse effects?	O Yes O No
B. Which medication	
Frequency (per day)	☐☐
Dosage (per day)	☐☐
Duration (length of treatment)	
Any adverse effects?	O Yes O No

3. Other	O Yes O No
A. Which medication	
Frequency (per day)	☐☐
Dosage (per day)	☐☐
Duration (length of treatment)	
Any adverse effects?	O Yes O No
B. Which medication	
Frequency (per day)	☐☐
Dosage (per day)	☐☐
Duration (length of treatment)	
Any adverse effects?	O Yes O No

Co-morbidities

	Parent question (based on 10Q Screen)*	**Formal assessment**
Physical	Does your child have any serious delay in sitting, standing or walking? O Yes O No Does your child have difficulty walking or	

	using arms or does he/ she have weakness in the arms/ legs? O Yes O No	
Epilepsy/ infantile seizures (date of onset) and seizure type	Does your child sometimes have fits, become rigid, or lose consciousness? O Yes O No	Date of onset (from above): Type of seizure (from above): Defined by 2 unprovoked seizures excluding febrile or neonatal seizures O Generalised or partial O Generalised – sudden onset of seizures that compromises responsiveness and affects the whole body O Partial – seizures have focality therefore symptoms reflect onset in 1 part of the brain
Visual impairment	Compared with other children, does your child have difficulty seeing, either in the daytime or at night? O Yes O No	O No O Diagnosed impaired O Suspected impaired O Unsure
Hearing impairment	Does your child appear to have difficulty hearing? O Yes O No	O No O Diagnosed impaired O Suspected impaired O Unsure
Intellectual impairment	Does your child learn to do things like other children his/ her age? O Yes O No Compared with other children of his/ her age, does your child appear in any way mentally backward, dull or slow? O Yes O No	O No O Diagnosed impaired O Suspected impaired O Unsure
Communication impairment	When you tell your child to do something, does he/ she seem to understand what you are saying? O Yes O No Does your child speak at all? O Yes O No Can your child name at least one object? O Yes O No	O No O Diagnosed impaired O Suspected impaired O Unsure

*10 Question Screen is a standardised parent-reported measure. Please ask these questions verbatim.

Part 2: Socio-demographic information

Household Characteristics

Family pedigree (3 generations) * Note this is not completed if biological caregiver is not involved and information is not recorded in the infant's medical record.	Any evidence of illness in the family; any problems with development or intellect; presence of motor disorder, congenital deformity, decreased motor function over time, in-utero/death, disease; cousin marriage, sudden/ unexplained death				
Family structure	2 caregivers (nuclear)	Separated parents dual custody	Cared for by other intact family	Single caregiver	Other
Birth order (of blood siblings	First born	Second born	Third born	Fourth born	Other (specify)
Child lives with	Nuclear family	Extended family	Step family	Kinship care	Foster care
Family members in the house (number)				Adult men	
				Adult women	
				Children <18 years	
Other relatives living close by	Yes / no				
Who regularly provides care for the child (multiple times per week)? (select as many as apply, and provide their details) Other (specify):	**Relationship to child:** Age: Highest education: Occupation: Frequency of care:	**Relationship to child:** Age: Highest education: Occupation: Frequency of care:	**Relationship to child:** Age: Highest education: Occupation: Frequency of care:	**Relationship to child:** Age: Highest education: Occupation: Frequency of care:	**Relationship to child:** Age: Highest education: Occupation: Frequency of care
Does the infant's biological mother/ father identify as	Aboriginal	Torres Strait Islander			
Primary language(s) spoken at home	English only Specify language(s):	Some English	No English		
Where family traditionally from?					
Current postcode					
Distance to town (corner store)	☐☐☐ minutes (in car)				

Employment

Who are the main earners/ workers in the family?	Grandfather	Grandmother	Father	Uncle	Mother	Other
Main earners' occupation/s						
Main earner's employment	Fulltime/ secure	Part-time/ casual	Unemployed/ pension		Fly in fly out	
Does ill-health often prevent them from working?	Y		N		NA	

Alcohol use in early pregnancy (AUDIT-C)*

Was the pregnancy planned or unplanned?	O Planned O Unplanned O Unknown
At what gestation did the mother realise she was pregnant?	Weeks O Unknown
Did the birth mother drink alcohol before the pregnancy was confirmed?	O No O Yes O Unknown
Did the birth mother modify her drinking behaviour on confirmation of pregnancy?	O Yes O No O Unknown
During which trimesters was alcohol consumed, tick all that apply	O None O 1st O 2nd O 3rd O Unknown
1. How often did the birth mother have a drink containing alcohol during this pregnancy?	O Unknown O Never (skip Qn 2 & 3) O monthly or less O 2-4 times a month O 2-3 times a week O 4 or more times a week
2. How many standard drinks did the birth mother have on a typical day when she was drinking this pregnancy?	O Unknown O 1 or 2 O 3 or 4 O 5 or 6 O 7 to 9 O 10 or more
3. How often did the birth mother have 5 or more standard drinks on one occasion during this pregnancy?	O Unknown O Never O Less than monthly O Monthly O Weekly O Daily or almost daily

* Note this is not completed if biological caregiver is not involved and information is not recorded in the infant's medical record.

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S2: LEAP- CP (Learning through Everyday Activities with Parents) _ 12-Month Medical Assessment- Differential Diagnosis

Study ID: ☐☐☐ **Date:** ☐☐/☐☐/☐☐☐☐

Completed by:

Child's name	
Corrected Age at assessment	
Weight	kg / percentile
Height	cm / percentile
Head Circumference	cm / percentile

Visual impairment (without correction, on both eyes)	Not assessed =0		Right (R=), Left (L=)
	Normal/No visual impairment =1		
	Squint =2		
	Impaired =3		
	Severely impaired (blind or no useful vision) =4		
Hearing impairment (before correction, on the better ear)	Not assessed =0		
	Normal =1		
	Impaired =2		
	Severely impaired (hearing loss > 70 dB) =3		
General Observation:	No abnormality =0	Abnormality=1	
Face	0	1	
dysmorphism	0	1	
general nutritional state	0	1	
Body proportions	0	1	
Muscle bulk	0	1	
symmetry	0	1	
tongue fasciculation	0	1	
excessive drooling	0	1	
other	0	1	
Gait:	Non ambulant = 0		**Comments:**
	Age appropriate = 1		
	Toe walking = 2		
	Asymmetrical gait = 3		

CEREBRAL PALSY

Motor type	**Primary**	**Secondary**
	Spastic =1	Spastic =1
	dyskinetic- dystonic =2	dyskinetic- dystonic =2
	dyskinetic- choreoathetotic =3	dyskinetic- choreoathetotic =3
	Hypotonic =4	Hypotonic =4
	Ataxic =5	Ataxic =5
Distribution	Bilateral =1 / unilateral =2	Bilateral =1 / unilateral =2
	No of limbs 1 / 2 / 3 / 4	No of limbs 1 / 2 / 3 / 4

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Neurological Signs:

Tone:	Left				Right			
Upper Limbs	Not tested = 0	Normal =1	Hypotonic =2	Hypertonic =3	Not tested = 0	Normal =1	Hypotonic =2	Hypertonic =3
Lower limbs	Not tested = 0	Normal =1	Hypotonic =2	Hypertonic =3	Not tested = 0	Normal =1	Hypotonic =2	Hypertonic =3

Tendon Reflexes:	Left	Right
Upper Limbs	Not tested =0 Present/Normal =1 Absent =2 Depressed =3 Brisk =4 Hyperreflexic/Very Brisk =5	Not tested =0 Present/Normal =1 Absent =2 Depressed =3 Brisk =4 Hyperreflexic/Very Brisk =5
Lower limbs	Not tested =0 Present/Normal =1 Absent =2 Depressed =3 Brisk =4 Hyperreflexic/Very Brisk =5	Not tested =0 Present/Normal =1 Absent =2 Depressed =3 Brisk =4 Hyperreflexic/Very Brisk =5

Clonus:						
Upper Limbs	Not tested = 0	Absent =1	Present =2	Not tested = 0	Absent =1	Present =2
Lower limbs	Not tested = 0	Absent =1	Present =2	Not tested = 0	Absent =1	Present =2

Plantar reflexes:							
Not tested = 0	Normal ↓ =1	No response =2	Abnormal ↑=3	Not tested = 0	Normal ↓ =1	No response =2	Abnormal ↑=3

Neurological Status	Normal = 0	Unspecified signs = 1	Abnormal (signs of CP) = 2

Cerebral palsy	No =0	High risk =1	Definitely =2	Unclear

Comments:

GMFCS level (0-2 years scale)	I =1 / II =2 / III =3 / IV= 4 / V= 5	
MACs level (1-4 year scale)	I =1 / II =2 / III =3 / IV= 4 / V= 5	
Upper limb/ Handedness	Right predominant =0 Left predominant =1 Bilateral =2	

FAS SYMPTOMOLOGY

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Sentinel Facial Features

Assess for the 3 sentinel facial features of Fetal Alcohol Spectrum Disorder: short palpebral fissure length (2 SD or more below the mean), smooth philtrum (rank 4 or 5 on the Lip-Philtrum guide), and thin upper lip (rank 4 or 5 on the Lip-Philtrum guide).

Palpebral Fissure Length (PFL)

	Right PFL		Left PFL		Mean PFL	
Assessment method	mm	Z score (SD)	mm	Z score	mm	Z score*
☐direct measure ☐ photo analysis						
☐direct measure ☐ photo analysis						
PFL reference chart used: ☐ Stromland ☐ Clarren ☐ Other						

Philtrum

Assessment method	UW Lip-Philtrum Guide 5-point rank
☐direct measure ☐ photo analysis	
☐direct measure ☐ photo analysis	
☐direct measure ☐ photo analysis	

Upper lip

Assessment method	UW Lip-Philtrum Guide 5-point rank
☐direct measure ☐ photo analysis	
☐direct measure ☐ photo analysis	
☐direct measure ☐ photo analysis	

Lip-Philtrum Guide† used: ☐ Guide 1. Caucasian ☐ Guide 2. African American

Sentinel Facial Features Summary

Number of Sentinel Facial Features (PFL 2 SD or more below the mean, philtrum rank 4 or 5, upper lip rank 4 or 5):

☐ 0 ☐ 1 ☐ 2 ☐ 3

Functional Neurodevelopmental Domain Summaries

Assess evidence of significant CNS dysfunction due to underlying brain damage. Required evidence includes severe neurodevelopmental impairment (2 SD or more below the mean or < the 3rd percentile) in domains of brain function based on standardised psychometric assessment by a qualified professional.

1. Neurological

Test/subtest name	Age/ Date	Score	%ile/SD	Interpretation
Other information:				
Motor Skills impairment: ☐ None ☐ Some ☐ Severe ☐ Not assessed				

2. Motor skills

Test/subtest name	Age/ Date	Score	%ile/SD	Interpretation
Other information:				
Motor Skills impairment: ☐ None ☐ Some ☐ Severe ☐ Not assessed				

3. Cognition

Test/subtest name	Age/ Date	Score	%ile/SD	Interpretation
Other information:				
Cognition impairment: ☐ None ☐ Some ☐ Severe ☐ Not assessed				

4. Language

(Expressive and Receptive)

Test/subtest name	Age/Date	Score	%ile/SD	Interpretation
Other information:				
Language impairment ☐ None ☐ Some ☐ Severe ☐ Not assessed				

5. Adaptive Behaviour, Social skills or Social Communication

Test/subtest name	Age/ Date	Score	%ile/SD	Interpretation
Other information:				
Adaptive behaviour, social skills, or social communication impairment ☐ None ☐ Some ☐ Severe ☐ Not assessed				

Neurodevelopmental Summary

Number of neurodevelopmental domains with evidence of severe impairment:

☐ None ☐ 1 ☐ 2 ☐ 3 or more(specify)

FAS	No =0	High risk of FAS =1	Definitely =2	Unclear

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ASD SYMPTOMOLOGY

Item	Score				
Visual Tracking	☐ 0	☐ 1	☐ 2		☐ 8
Disengagement of attentions	☐ 0	☐ 1	☐ 2		☐ 8
Orientation to name	☐ 0	☐ 1	☐ 2		☐ 8
Differential response to facial emotion	☐ 0	☐ 1	☐ 2		☐ 8
Anticipatory social response	☐ 0	☐ 1	☐ 2	☐ 3	☐ 8
Imitation	☐ 0	☐ 1	☐ 2		☐ 8
Social Babbing	☐ 0	☐ 1	☐ 2	☐ 3	☐ 8
Eye Contact	☐ 0		☐ 2		☐ 8
Reciprocal social smile	☐ 0	☐ 1	☐ 2	☐ 3	☐ 8
Coordination of eye gaze	☐ 0	☐ 1	☐ 2	☐ 3	☐ 8
Behavioural Reactivity	☐ 0	☐ 1	☐ 2	☐ 3	☐ 8
Social interest and shared affect	☐ 0	☐ 1	☐ 2	☐ 3	☐ 8
Transitions	☐ 0	☐ 1	☐ 2		☐ 8
Motor control	☐ 0	☐ 1	☐ 2		☐ 8
Atypical motor behaviour	☐ 0		☐ 2		☐ 8
Engagement of attention	☐ 0	☐ 1	☐ 2		☐ 8
Insistence on specific objects/activities	☐ 0	☐ 1	☐ 2		☐ 8
Sharing Interest	☐ 0	☐ 1	☐ 2		☐ 8
Total score					

ASD	No =0	High risk of ASD =1	Definitely =2	Unclear

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12-Month Medical Assessment- Blinded Differential Diagnosis

Study ID: ☐☐☐ **Date:** ☐☐/☐☐/☐☐☐☐

Completed by:

Cerebral palsy	No =0	High risk =1	Definitely =2	Unclear
Motor type	**Primary**		**Secondary**	
	Spastic =1		Spastic =1	
	dyskinetic- dystonic =2		dyskinetic- dystonic =2	
	dyskinetic- choreoathetotic =3		dyskinetic- choreoathetotic =3	
	Hypotonic =4		Hypotonic =4	
	Ataxic =5		Ataxic =5	
Distribution	Bilateral =1 / unilateral =2		Bilateral =1 / unilateral =2	
	No of limbs 1 / 2 / 3 / 4		No of limbs 1 / 2 / 3 / 4	
GMFCS level (0-2 years scale)	I =1 / II =2 / III =3 / IV= 4 / V= 5			
MACs level (1-4 year scale)	I =1 / II =2 / III =3 / IV= 4 / V= 5			
Comments				

FAS	No =0	High risk of FAS =1	Definitely =2	Unclear
Comments				

ASD	No =0	High risk of ASD =1	Definitely =2	Unclear
Comments				

S3: LEAP – CP Medical and Allied Health Resource Form

Study ID: ☐☐☐ **Date:** ☐☐/☐☐/☐☐☐☐
Form completed by: **Interviewer initials:** ☐☐

Allied Health

During the last 6 months have you received treatment or advice from:

1. Physiotherapy	O Yes O No
Does it emphasise	O Motor learning O Equipment O Functional therapy O Stretching & positioning O Other: _____
How often	☐☐ Visits per 6 months
Format	O Individual O Group O Home program
Location	O Hospital O Community O Home O Private practice

2. Occupational therapy	O Yes O No
Does it emphasise	O Motor learning O Equipment O Functional therapy O Stretching & positioning O Other: _____
How often	☐☐ Visits per 6 months
Format	O Individual O Group O Home program
Location	O Hospital O Community O Home O Private practice

3. Speech therapy	O Yes O No
Does it emphasise	O Speech/ talking O Early communication skills (play) O Sign/ symbol O Mealtime O Other: _____
How often	☐☐ Visits per 6 months
Format	O Individual O Group O Home program
Location	O Hospital O Community O Home O Private practice

4. Other	O Yes O No
What does it emphasise?	
How often	☐☐ Visits per 6 months
Format	O Individual O Group O Home program
Location	O Hospital O Community O Home O Private practice

Medical

During the last fortnight, has your child been sick? O Yes ☐☐ (number of days) O No

During the 6 months, has your child had:

1. Admission to hospital	O Yes O No Number of admissions ☐
Visit 1	Reason: Treatment/ investigation: Length of stay ☐☐ days
Visit 2	Reason: Treatment/ investigation: Length of stay ☐☐ days
Visit 3	Reason: Treatment/ investigation: Length of stay ☐☐ days
Visit 4	Reason: Treatment/ investigation: Length of stay ☐☐ days

2. GP appointment	O Yes O No Number of appointments ☐
Visit 1	Reason: Treatment/ investigation:
Visit 2	Reason: Treatment/ investigation:
Visit 3	Reason: Treatment/ investigation:

Visit 4	Reason: Treatment/ investigation:

3. Paediatrician	O Yes O No Number of appointments ☐
Visit 1	Reason: Treatment/ investigation:
Visit 2	Reason: Treatment/ investigation:
Visit 3	Reason: Treatment/ investigation:
Visit 4	Reason: Treatment/ investigation:

4. Other specialist Who:	O Yes O No Number of appointments ☐
Visit 1	Reason: Treatment/ investigation:
Visit 2	Reason: Treatment/ investigation:
Visit 3	Reason: Treatment/ investigation:
Visit 4	Reason: Treatment/ investigation:

5. Other specialist Who:	O Yes O No Number of appointments ☐
Visit 1	Reason: Treatment/ investigation:
Visit 2	Reason: Treatment/ investigation:
Visit 3	Reason: Treatment/ investigation:
Visit 4	Reason: Treatment/ investigation:

6. Other specialist Who:	O Yes O No Number of appointments ☐
Visit 1	Reason: Treatment/ investigation:
Visit 2	Reason: Treatment/ investigation:
Visit 3	Reason: Treatment/ investigation:
Visit 4	Reason: Treatment/ investigation:

Equipment

Has your child been provided with any equipment:

- ☐ Supportive chair/ seating
- ☐ Walking aids
- ☐ standing frame
- ☐ Splints / orthoses
- ☐ Wheelchair

National Disability Insurance Scheme (NDIS) Funding

Does your child have an NDIS plan?	O Yes O No
Is the plan self managed?	O Yes O No
What are you able to use your funding for?	O Therapy (eg physiotherapy, OT) O Equipment (eg walking aid/ orthoses) O Consumables (eg feeding tubes)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1 and 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3-7
Objectives	3	State specific objectives, including any prespecified hypotheses	7-9
Methods			
Study design	4	Present key elements of study design early in the paper	9
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	9-13
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	10-13
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	10, 13-20,
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	13-20
Bias	9	Describe any efforts to address potential sources of bias	21
Study size	10	Explain how the study size was arrived at	10-11
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	20-21
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	20
		(*b*) Describe any methods used to examine subgroups and interactions	20
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	20
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	20
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	Report numbers of outcome events or summary measures over time	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	20
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	20
Discussion			
Key results	18	Summarise key results with reference to study objectives	
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	
Generalisability	21	Discuss the generalisability (external validity) of the study results	
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	24

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Study Protocol: Early detection of Australian Aboriginal and Torres Strait Islander infants at high risk of adverse neurodevelopmental outcomes at 12 months corrected age: LEAP-CP prospective cohort study

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Secondary Subject Heading:	Rehabilitation medicine, Neurology
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Study Protocol: Early detection of Australian Aboriginal and Torres Strait Islander infants at high risk of adverse neurodevelopmental outcomes at 12 months corrected age: LEAP-CP prospective cohort study

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Number of Tables: 1

ABSTRACT

Introduction Neurodevelopmental disorders (NDD) including; cerebral palsy (CP), autism spectrum disorder (ASD) and fetal alcohol spectrum disorder (FASD), are characterised by impaired development of the early central nervous system, impacting cognitive and/or physical function. Early detection of NDD enables infants to be fast-tracked to early intervention services, optimising outcomes. Aboriginal and Torres Strait Islander infants may experience early life factors increasing their risk of neurodevelopmental vulnerability, which persist into later childhood, further compounding the health inequities experienced by First Nations peoples in Australia.

The LEAP-CP prospective cohort study will investigate the efficacy of early screening programs, implemented in Queensland, Australia to earlier identify Aboriginal and Torres Strait Islander infants who are 'at risk' of adverse neurodevelopmental outcomes (NDO) or NDD. Diagnostic accuracy and feasibility of early detection tools for identifying infants 'at risk' of a later diagnosis of adverse NDO or NDD will be determined.

Methods and Analysis Aboriginal and/ or Torres Strait Islander infants born in Queensland, Australia (birth years 2020-2022) will be invited to participate. Infants aged ≤9 months corrected age (CA) will undergo screening using the: (i) General Movements Assessment (GMA); (ii) Hammersmith Infant Neurological Examination (HINE); (iii) Rapid Neurodevelopmental Assessment (RNDA) and (iv) Ages and Stages Questionnaire - Aboriginal adaptation (ASQ-TRAK). Developmental outcomes at 12 months CA will be determined for: (i) neurological (HINE); (ii) motor (Peabody Developmental Motor Scales 2); (iii) cognitive and communication (Bayley Scales of Infant Development III); (iv) functional capabilities (Pediatric Evaluation of Disability Inventory - computer adaptive test); and (v) behaviour (Infant Toddler Social and Emotional Assessment). Infants will be classified as typically developing or 'at risk' of an adverse NDO and/or specific NDD based on symptomology using developmental and diagnostic outcomes for (i) CP (ii) ASD and (ii) FASD. The effects of perinatal, social and environmental factors, caregiver mental health and clinical neuroimaging on neurodevelopmental outcomes will be investigated.

Ethics and Dissemination Ethics approval has been granted by appropriate Queensland ethics committees; Far North Queensland Health Research Ethics Committee (HREC/2019/QCH/50533 (Sep ver 2) - 1370), the Townsville HHS Human Research Ethics Committee (HREC/QTHS/56008), the University of Queensland Medical Research Ethics Committee (2020000185/HREC/2019/QCH/50533), and the Children's Health Queensland HHS Human Research Ethics Committee (HREC/20/QCHQ/63906) with governance and support from local First Nations communities. Findings from this study will be disseminated via peer-reviewed publications and conference presentations.

Trial registration number ACTRN12619000969167

Key words: Indigenous, Aboriginal and Torres Strait Islander, infant, prospective cohort study, clinical assessment tools, neurodevelopmental outcomes, neonatal screening, cerebral palsy, autism spectrum disorder, fetal alcohol spectrum disorder

Strengths and limitations of this study:

- This prospective population-based cohort study investigates the use of standardised screening tools to predict a later diagnosis of adverse neurodevelopmental outcomes in an Australian Aboriginal and Torres Strait Islander birth cohort.
- Capacity building of local services and use of technology ensures infants and families can readily access gold standard screening programs close to home.
- Community and stakeholder engagement, knowledge sharing and co-design promotes access to culturally sensitive programs.

- The remote locality of many Indigenous communities in Australia may present challenges, limiting access to health services and impacting loss to follow-up of infants at study outcome timelines.

INTRODUCTION

In Australia, Aboriginal and Torres Strait Islander peoples, are among the most disadvantaged across all domains. In acknowledgement of the unique and distinct countries, cultures and languages of Australian First Nations people, the term 'Indigenous' is respectfully used herein to encompass but not homogenise the diverse identities of Aboriginal and Torres Strait Islander peoples.

Ongoing intergenerational trauma, systematic displacement from traditional lands, loss of culture and racism experienced by Australian Indigenous people continues to manifest in socio-economic disadvantage, marginalisation, reduced education and employment opportunities, leading to poorer health outcomes[1,2]. Indigenous Australians are 1.8 times more likely to experience disability, twice as likely to have a severe disability and are less likely to access support[3] compared to non-indigenous Australians[4,5]. Inequities in access to culturally safe health and disability support services[6], long waiting lists and the rurality of some Indigenous communities, further compounds this disadvantage[7,8]. These factors have contributed to a significant gap in health outcomes between Indigenous and non-Indigenous Australians[3,9].

Indigenous children, living in urban, rural and remote Australia, have an increased risk of adverse Neurodevelopmental Outcomes (NDO). This can include being at risk for a range of specific childhood neurodevelopmental disorders (NDD): Cerebral Palsy (CP), Fetal Alcohol Spectrum Disorder (FASD), and Autism Spectrum Disorder (ASD)[8,10,11]. These conditions are characterised by impaired development of the early central nervous system, resulting in cognitive and/or physical disability[12,13]. Indigenous children are 30% more likely to have a physical disability, and are at higher risk of developmental and intellectual difficulties, compared to non-Indigenous children[11,14,15]. The prevalence of NDDs in some remote communities are reported to be as high as 30% of the paediatric population[10].

Indigenous infant early life risk factors

Many Australian Indigenous infants can experience a range of perinatal, maternal, post-neonatal (PNN) and socioeconomic risk factors that increase their risk of later adverse NDOs. While the neonatal death rate for Indigenous infants has declined, the rates of preterm birth (i.e., <37 weeks GA), low birth weight (LBW; i.e., <2500g) and small for gestational age (SGA) births has remained relatively stable[16]. In 2018, infants of Indigenous mothers were 65 percent more likely to be born pre-term, 87 percent more likely to be LBW and 52 percent more likely to be SGA, compared to babies of non-Indigenous mothers[16]. In addition, 28 percent of Indigenous infants were admitted to the neonatal intensive care unit (NICU) or special care nursery (SCN), requiring specialised medical treatment[16].

Improving Indigenous birth outcomes, including preterm birth and LBW, is a national priority for the Australian Closing the Gap Agenda[17]. Infants born pre-term and with LBW have an increased risk of adverse NDOs, which can influence school readiness and academic achievement[18-22]. Biological and environmental risk factors impact birth outcomes and are

associated with increased risk of developmental vulnerability[14,23-25]. These factors are compounded by remote locality, access to appropriate and culturally sensitive antenatal care, and, socioeconomic disadvantage[23-25]. Maternal factors including age, education, health, smoking and substance use have been linked to poorer birth outcomes[14,24,25]. In Australia, Indigenous mothers are more likely to be younger, single, attain lower levels of education, live in lower socio-economic circumstances and have lower rates of attendance at antenatal care[16,25]. Emerging evidence demonstrates the protective impact of culturally led[26] birthing programs which have led to an improved uptake in antenatal care and smoking cessation, subsequently lowering the risk of neonatal and adverse developmental outcomes[26-29].

The cultural, geographical and socio-economic barriers to healthcare access experienced by Indigenous Australians can lead to delayed identification of infants at risk of adverse NDOs with subsequent delays in receiving early intervention to optimise outcomes[11,30]. While there is consensus that early detection is important for all adverse NDOs, variability exists in the recommendations for the screening and diagnosis of CP, ASD and FASD.

Neurodevelopmental Disorders (NDD)

NDDs are characterised by distinct clinical manifestations and symptomology. A transdiagnostic approach supports the notion that many NDDs share similar early markers and comorbidities across multiple neurodevelopmental domains[31-33]. Targeted early screening programs should aim to identify an infant's risk status for a range of adverse NDOs which may predict a later specific diagnosis[32,34]. Differences in quality of movement, atypical motor development, and cognition are common early risk attributes and neurodevelopmental features of CP, ASD and FASD[10,35-39].We hypothesise that valid and reliable predictive tools utilised for the detection of CP may also identify early neurodevelopmental vulnerabilities in infants at risk of a later diagnosis of ASD and FASD and/or other substantial developmental delays.

Cerebral Palsy (CP)

Cerebral Palsy, the most common physical disability of childhood (1 in 700 live births)[40], is defined as a developmental disorder of movement and posture attributed to non-progressive disturbances in the developing brain that occur in early infancy, impacting function, participation and self-care[41]. Injury to the developing brain can occur pre-, peri-, or post-neonatally, due to a recognised event associated with brain damage[8].

Improvements in medical care and neuroprotective interventions for preterm birth, LBW and other pregnancy complications have been associated with a decline in the overall rate of CP[42]. Advances in early detection, diagnosis, prevention and intervention in high resource countries have additionally led to improvements in CP prognosis and decreased incidence[42,43]. In Australia, the trend in declining CP rates has demonstrated a decrease in incidence from 1 in 500 children to 1 in 700 children and a reduction in severity of motor function, with more children ambulant[40,43].

International Clinical Practice Guidelines support a confirmed or 'high risk' of CP diagnosis prior to 6 months CA[44]; however the age of diagnosis of CP in high income

countries still occurs relatively late, usually between 12 to 24 months, delaying access to early intervention services[44]. The use of gold standard clinical assessments, such as Prechtl's Qualitative Assessment of General Movements (GMA), the Hammersmith Infant Neurological Examination (HINE) and Magnetic Resonance Imaging (MRI), are recommended for reliable and accurate prediction of 'high risk' of CP[44,45]. Individually these tools are highly sensitive, however a combined abnormal MRI and trajectory of abnormal GMA and HINE scores demonstrates the greatest diagnostic accuracy (97.8% sensitivity and 99.2% specificity) at 3 months CA[46]. The GMA evaluates the quality of an infant's early spontaneous movement patterns, which reflects central nervous system integrity and function[47,48]. An abnormal/absent GMA at 3 months CA is highly predictive of CP in 'high risk' infants[45], and may be a marker for other adverse NDOs[35,47,49-51]. Due to the time-sensitive nature of the GMA (at 11-17 weeks CA), the HINE is recommended to assess an infant's neurological development between 3-24 months CA[44]. The HINE also provides insight into CP topography (unilateral vs bilateral)[52,53] and severity (ambulant vs non-ambulant, GMFCS I-III vs IV-V)[54-58]. While the GMA and HINE are relatively easy to administer, trained clinicians are required to evaluate and interpret scores.

In Australia, the rate of CP is estimated to be 50 percent higher for Indigenous children[8], with the rate of pre- or perinatally acquired CP almost three times that of non-Indigenous infants[59]. Indigenous infants with CP are more likely to be born extremely pre-term (<28 weeks) and LBW than non-Indigenous infants with CP, increasing their risk of functional severity[8,60]. Indigenous infants are five times more likely to acquire CP post-neonatally, which is associated with an increased severity of CP and linked to socioeconomic conditions[8,23,40]. In addition to higher rates of CP diagnosis, Indigenous children with CP have poorer cognitive and gross motor outcomes and a higher proportion of comorbidities, being twice as likely to have visual impairments and 50 percent have a co-diagnosis of epilepsy[8,59]. Accurate Australian data pertaining to the prevalence of CP, age of diagnosis, rates of referral and access to early intervention in Indigenous infants remains unknown.

Autism Spectrum Disorder (ASD)

Autism spectrum disorder (ASD) describes a group of heterogeneous NDDs characterised by core difficulties with social interaction and the presence of restrictive and repetitive patterns of interest or behaviours[61]. Many individuals with ASD demonstrate associated impairments in cognition, challenging behaviours, communication and motor function[38,62]. With a 42 percent increase in prevalence from 2015 to 2018 in Australia[63] the diagnosis of ASD continues to be commonly made after two years and frequently not until school age (i.e. average six years;[64]), limiting timely early intervention[65].

Early motor abnormalities[38,39,66-68], reduced verbal skills, differences in social interactions[69,70] and ASD-related infant behaviours may be detected in children with ASD from 6 months CA; however, there are few ASD screening and diagnostic tools for infants <12 months of age[70,71]. The Autism Observational Schedule in Infants (AOSI) evaluates the presence of ASD-related behaviours, in infants aged 6-18 months[71-74]. Elevated AOSI scores at 12 and 18 months CA are associated with ASD diagnosis at 2 and 3 years of age, and are predictive of social-communication difficulties in high risk infants at 2 years[72-75]. Atypical responses to specific test items, including eye contact, social interest and orienting to

name are discriminative between high risk infants with a subsequent diagnosis, high risk infants without subsequent diagnosis and low risk infants[74,76]. Differences in infant motor development[67,68,77] and the quality of early infant movements may provide additional insights into ASD-related outcomes[35,47,51,78]. Studies investigating use of GMA for prediction of ASD in high risk infants, identified that >60 percent of children with a later confirmed diagnosis had abnormal or absent fidgety movements at 12-16 weeks of age[35,51,78]. Universal screening tools such as the Ages and Stages Questionnaire (ASQ;[79]) and the Rapid Neurodevelopmental Assessment (RNDA;[80]) identify infants with atypical cognitive, social and communication development, but require further investigation regarding the predictive ability of ASD-related behaviours.

There is a paucity of data relating to the prevalence of ASD in Australian Indigenous populations[81]. While some studies have investigated the incidence of ASD and intellectual disability among specific Indigenous communities, accurate prevalence remains relatively unknown, with reported inconsistencies impacted by differences in cultural conceptualisation of disability, misdiagnosis, and decreased awareness of ASD among Indigenous communities[3,15,64,81-84]. There is growing concern that Indigenous children are misdiagnosed or missing out on an ASD diagnosis[6,83], supporting the need for culturally sensitive early diagnostic tools and services.

Fetal Alcohol Spectrum Disorder (FASD)

Alcohol exposure in utero can result in adverse outcomes across multiple neurodevelopmental domains including: cognition, motor skills, brain structure, language, academic achievement, attention, and adaptive behaviour[85-87]. Fetal Alcohol Spectrum disorder (FASD) is the diagnostic term used for individuals who are exposed to alcohol prenatally and demonstrate severe impairment in 3 or more neurodevelopmental domains[86,88]. Diagnosis according to the Australian Guide is categorised as either; FASD with 3 sentinel facial features or FASD with < 3 sentinel facial features, indicating the presence or absence of facial dysmorphology specific to prenatal alcohol exposure (PAE) in the first trimester[86,87]. The co-existence of multiple comorbidities can complicate FASD diagnosis and further impact the long term sequalae[89]. FASD can be associated with an increased risk of physical health conditions[90], poor mental health, substance misuse, and involvement in the criminal justice system[91]. These lifelong consequences are extremely costly to the individual, family, health, education, disability and justice systems[92,93].

The Australian Guide to the assessment and diagnosis of FASD[88] recommends early intervention, however early diagnosis and provision of appropriate treatment strategies are under-developed[94]. In the absence of facial dysmorphology, there are few accurate early biomarkers for infants at risk of FASD[85,88,89,95]. Diagnostic assessments are complex, time consuming, and require a multidisciplinary team of specialised clinicians[87,96]. Furthermore, most of the recommended standardised neurodevelopmental assessments are for children >2 years[88]. The use of standardised screening tools <6 months CA, such as GMA and HINE may enable the accurate detection of neurodevelopmental delay, which could lead to earlier diagnosis of FASD.

The reported prevalence of FASD and patterns of PAE in Australia are variable, due to complexities with missed or misdiagnosis, practitioners not enquiring about prenatal alcohol

use, and availability of diagnostic services[94,96,97]. In Australia, rates of FASD in some Indigenous populations are among the highest globally, impacted by the interplay of biological and psychosocial risk factors[10,97,98]. In one remote community 19 percent of school-aged children had a FASD diagnosis, 25 times higher than the global rate[98,99]. Furthermore, the prevalence of FASD (47 percent) among Aboriginal young people (13-17 years) in custody in WA is almost 6 times higher than that of non-Indigenous adolescents in custody[97]. The subsequent effect of PAE on developmental trajectory underpins the need for culturally sensitive, early screening tools to enable detection of infants who are high risk of FASD.

While there is emerging data on the prevalence and profile of adverse NDOs and NDDs in the Indigenous population[8,10,14,15,27,100] the focus has been on diagnosis of specific NDDs in early childhood. The aim of this cohort study is to investigate the use of early standardised screening tools (such as GMA, HINE) to determine risk status of infants aged ≤12 months CA, for a later diagnosis of CP, ASD, FASD and/or other substantial developmental delay in an 'at risk' Australian Indigenous birth cohort.

OVERVIEW OF AIMS

Broad Aim

The primary aim of the current study is to investigate the impact of early screening for Indigenous infants at risk of adverse NDOs due to prenatal, birth and early life factors, in terms of:

i. Diagnostic accuracy, clinical utility and cultural appropriateness of early infant neurodevelopmental assessments to accurately predict a later 'at risk' diagnosis at 12 months CA.

ii. Impact of perinatal variables, maternal factors and caregiver mental health on the developmental outcomes of Indigenous infants at risk of adverse NDOs in Queensland.

A comprehensive list of study aims and hypotheses are outlined in Table 1.

Table 1: LEAP-CP: Early detection study aims and hypotheses

AIM 1 To determine the predictive accuracy, of the General Movements Assessment (GMA), the General Movements Motor Optimality Score (MOS), the Hammersmith Infant Neurological Examination (HINE), the Rapid Neurodevelopmental Assessment (RNDA), and the Ages and Stages – aboriginal adaptation (ASQ-TRAK) to predict a later outcome at 12 months CA of 'at high risk' of (i) CP or (ii) Adverse Neurodevelopmental Outcome (non-CP) or (iii) Typically developing in Indigenous infants.	
H1a	Sensitivity to detect CP at 12 months CA in Indigenous infants will be >98% for abnormal GMA (Absent Fidgety, Abnormal Fidgety) at 3 months CA and >90% for suboptimal HINE score (<60 and/or ≥5 asymmetries) at 6 months CA.
H1b	Specificity to detect CP at 12 months CA in Indigenous infants will be >90% for abnormal GMA (Absent Fidgety, Abnormal Fidgety) at 3 months CA and >85% for suboptimal HINE score (<60 and/or ≥5 asymmetries) at 6 months CA.
H1c	Indigenous infants with a confirmed or 'at risk' diagnosis of CP at 12 months will have a motor optimality score (MOS) between 8 and 14 (GMFCS I-III) or <8 (GMFCS IV and V) at 3-5 months CA, infants with a diagnosis of 'at risk' of adverse NDOs (non-CP) at 12 months CA will have a MOS <21 at 3-5 months CA.

H1d	The sensitivity and specificity of the GMA and MOS to detect an adverse NDO (non-CP) at 12 months CA will be less than that of CP.
H1e	Sensitivity and specificity to detect adverse NDOs (non-CP) at 12 months CA will be ≥81% and ≥71% respectively for suboptimal HINE score (<65) at 6 months or (<70) at 9 months CA.
H1f	Indigenous infants who score 'at risk' on ≥1 domain the ASQ-TRAK at 6 months CA (domain specific cut offs gross motor<23, fine motor <26, communication<30, problem-solving<28, personal-social<26) will have a diagnosis of 'at risk' of adverse NDOs (non-CP) and/or CP at 12 months CA.
H1g	Indigenous infants who score moderate to severe on any domain of the RNDA at 6 months CA will have good to excellent specificity (>0.8) compared to poor to fair sensitivity (0.6-0.8) to detect 'at risk' of CP and/or adverse NDOs (non-CP) at 12 months CA.
AIM 2 To determine the neurological (HINE), motor (PDMS-2), cognitive (BSID-III), developmental (PEDI-CAT/ASQ-TRAK) and behavioural (ITSEA) profiles of Indigenous infants with a diagnosis of 'at risk' of specific NDDs (i) CP, (ii) ASD, (iii) FASD, and/or (iv) adverse NDO (non-specific) or (v) typically developing/borderline at 12 months CA compared to normative data.	
H2a	Indigenous infants at high risk of CP at 12 months CA will score HINE<70 (GMFCS I-III), or ≤40 (GMFCS IV-V); BSID-III >2SD below the mean (50% cognitive scale, 25% communication scale), PDMS-2 >1 SD below the mean (GMFCS I- III) or >2 SD below the mean (GMFCS IV-V) and PEDI-CAT >1SD below the mean (GMFCS I-III) or >2 SD below the mean (GMFCS IV-V) (mobility scale).
H2b	Indigenous infants with ASD symptomology at 12 months CA will have a greater number of risk markers on the AOSI and/or will score HINE <70, on average score >1 SD below the mean on the BSID-III (communication scale, cognitive scale), and PDMS-2, PEDI-CAT >2 SD below the mean (personal/social scale), ITSEA ≥1.5 SD below the mean (competence domain) and/or ≥1.5 SD above the mean (externalising, internalising, dysregulation domains).
H2c	Indigenous infants with FASD symptomology at 12 months CA will have microcephaly, ≤3 sentinel facial features and significant impairment (≥2 SD below the mean or equivalent) on ≥3 developmental domains including motor (PDMS-2 total motor quotient, PEDI-CAT mobility), neurological (<70 on the HINE), cognitive (BSID-III cognitive subscale, PEDI-CAT daily activities), communication (BSID-III language composite score), Adaptive behaviour/social skills (PEDI-CAT personal/social scales, ITSEA subdomains).
H2d	Indigenous infants at risk of adverse NDOs (non-specific) at 12 months will have significant impairment (>2 SD below the mean) on 1 domain and/or or mild to moderate impairment (>1SD below mean) in ≥2 domains including motor (PDMS-2 total motor quotient, PEDI-CAT mobility), neurological (<70 on the HINE), cognitive (BSID-III cognitive subscale, PEDI-CAT daily activities), communication (BSID-III language composite score), Adaptive behaviour/social skills (PEDI-CAT personal/social scales, ITSEA).
H2e	Indigenous infants typically developing (≤1SD below the mean or equivalent on all developmental domains) or borderline (mild delay; between 1 and 2SD below the mean on 1 domain) at 12 months CA will score >70 on the HINE (neurological), and ≤1 SD below the mean on the PDMS-2, BSID-III, PEDI-CAT and ITSEA (motor, cognition, communication, self-care and personal/social scales, behaviour).
AIM 3 To determine the clinimetric properties of outcome and/or predictive measures used to assess a cohort of 'at risk' Indigenous infants (GMA, HINE, RNDA, ASQ-TRAK, BSID-III, PDMS-2, PEDI-CAT, ITSEA) in terms of (i) construct validity, (ii) reliability, (iii) cultural acceptability and (iv) clinical utility/feasibility.	

H3a	Indigenous infants who are assessed to have ≥2 neurodevelopmental impairments (NDI) and/or score moderate to severe impairment on any domain of the RNDA at 6 months and 12 months CA will have suboptimal HINE scores at 6 (<65) and 12 (<70) months CA.
H3b	Indigenous infants who score 'at risk' on the communication (<16) and/or problem-solving (<28) domains of the ASQ-TRAK at 12 months CA will score ≥2SD below the mean on the language and/or cognitive domains of the BSID-III at 12 months CA.
H3c	Indigenous infants who score 'at risk' on the gross motor (<22) and/or fine motor (<35) domains of the ASQ-TRAK at 12 months CA will score ≥2SD below the mean on the Gross Motor and/or Fine Motor Quotients of the PDMS-2 at 12 months CA.
H3d	Indigenous infants who score 'at risk' on the personal-social (<22) domain of the ASQ-TRAK at 12 months CA will score ≥2SD below the mean on the corresponding domain of the PEDI-CAT and ITSEA at 12 months CA.
H3e	There will be strong interrater reliability and agreement (k>0.8) between clinicians and community health workers for the HINE, RNDA and ASQ-TRAK.
H3f	The clinical utility and cultural acceptability of screening tools used to predict later neurodevelopmental outcomes of Indigenous infants at ≤9 months (GMA, HINE, RNDA and ASQ-TRAK) will be higher than that of tools used to measure developmental outcomes at 12 months CA (PDMS-2, BSID-III, PEDI-CAT, ITSEA).
AIM 4 To determine the relationship between (i) perinatal variables, (ii) maternal risk factors and outcomes of (i) motor, (ii) cognition and (iii) development for Indigenous infants at 12 months CA.	
H4a	Adverse perinatal variables including, gestational age (<37weeks) , low birthweight (<2500g), events that signify complications during labour and delivery, adverse neonatal medical complications, and post-neonatal events including, infection, non-accidental injury, cerebro-vascular accident, will be significantly associated with lower scores on neurological, motor, cognitive, developmental and behavioural assessments at 12 months CA (HINE, PDMS-2, BSID-III, ASQ-TRAK, PEDI-CAT, RNDA, ITSEA).
H4b	Maternal risk factors (significant maternal medical conditions, antenatal medical complications and treatment, antenatal substance use and social risk factors as determined by the Social Risk Index), will be associated with lower scores on neurological, motor, cognitive, developmental and behavioural assessments at 12 months CA (HINE, PDMS-2, BSID-III, ASQ-TRAK, PEDI-CAT, RNDA, ITSEA).
H4c	Elevated caregiver stress, anxiety and depression on the DASS-21 will be associated with lower scores on neurological, motor, cognitive, developmental and behavioural measures in Indigenous infants at 12 months CA (HINE, PDMS-2, BSID-III, ASQ-TRAK PEDI-CAT, RNDA, ITSEA).

METHODS

Study Design

This multi-site prospective cohort study of 120 Indigenous infants will be conducted in Queensland, Australia, commencing in 2021 and will run for two years, with planned completion for 2023. The methodological design follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines[101].

Participants

A cohort of 120 Indigenous infants with identified risk factors for adverse NDOs will be recruited. Recruitment will occur over an 18-month period (birth years 2020-2022) from the

Neonatal Intensive Care Unit (NICU), Special Care Nurseries (SCN), Paediatric wards and outpatient clinics across Queensland.

Inclusion Criteria

Infants eligible for screening will be those aged 0-9 months CA with one or both biological parents identifying as Aboriginal and/or Torres Strait Islander, who meet the following criteria:

(i) pregnancy complications, LBW (<2500g), born preterm (<37 weeks gestation), or at term with Hypoxic Ischemic Encephalopathy (HIE), 5 min Apgar <6, history of neurological risk factors (e.g., admission to NICU/SCN, congenital abnormalities, SGA, seizures), post-neonatal complications (e.g., head injury, stroke, infection, non-accidental injury), maternal risk factors that may impact neonatal outcomes (e.g. medical conditions, , antenatal substance use) or family history of adverse NDOs and/or sibling with a diagnosed NDD.

(ii) reside in Queensland.

Exclusion Criteria

Infants with major congenital or chromosomal abnormalities identified as part of routine medical care.

Recruitment procedures

Infants will be recruited through Queensland Hospital and Health services (HHS) and Aboriginal Community Controlled Health Organisations with ethics and governance approvals in place (see acknowledgments). The study will be introduced to parents or caregivers of infants who meet eligibility criteria by an Indigenous Liaison Officer (ILO) or member of staff from the recruiting sites. If families are interested in participating and consent to being contacted, a member of the research team will contact the family and provide information regarding the study, including a culturally adapted parent information statement. The research team member, who is not associated with the infant's care, will explain the study in more detail and answer all parent questions prior to seeking informed consent for study participation. Families will be given the option to verbally discuss the parent information sheet with an ILO or Indigenous Community Health Worker (CHW) prior to providing written informed consent to participate. Once signed consent is obtained, the infant will be enrolled in the study and will commence the relevant screening assessments.

Sample Size

This study aims to predict a later diagnosis of (i) typical development or 'at risk' of specific NDD, (ii) CP, (iii) ASD, (iv) FASD and/or (v) adverse NDO (non-specific) in a population of Indigenous infants with known exposure to early life risk factors. The projected sample size of 120 Indigenous infants is based on the expected number of new diagnoses of CP, ASD, FASD or adverse NDOs over an 18-month period at the study sites. The Cairns and Townsville hospitals have a potential combined total of 1400 infants admitted to their NICU and SCN's per year. Approximately 38 percent (n=540) of these infants have one or both biological parents who identify as Indigenous. The proportion of participating children with an adverse NDO we are likely to observe in the LEAP-CP cohort has been estimated by combining data from

Australian data registers with data from a retrospective audit of a cohort of high risk infants admitted to the Townsville Hospital NICU or SCN during 2019-2020.

The Western Australia Cerebral Palsy register is the register that has reported rates of CP in Indigenous children for the longest duration and has a current estimate of 4.01 CP cases per 1000 births. Incidence of ASD in Indigenous Australian children is hypothesised to be approximately equal non-Indigenous rates, at between 7 and 15 ASD cases per 1000 births[6,81]. Incidence of FASD in Indigenous Australians is estimated at 17 FASD cases per 1000[102], but could be as much as 10-times higher in some remote communities[98]. The overall number of Indigenous children who have either developmental delay or an adverse NDO may range from 10% in low risk cohorts[14] to 30% in high risk remote communities[10].

A retrospective audit of high-risk Indigenous children admitted to the Townsville Hospital neonatal unit or SCN identified 16 children with known outcomes at 12 - 24 months CA. Of these children, 25 percent were at high risk of CP, 25 percent were at risk of a non-CP NDO, 31 percent had a non-neuromotor delay while 19 percent had no neurodevelopmental concerns. Overall >80 percent of these children were classed as having at least mild delay, although it should be noted that these children were at higher risk for an NDO than those who will participate in the LEAP-CP cohort. For the 120 children recruited to the LEAP-CP cohort we estimate approximately one-third (33 percent) will be identified as being at risk of an NDO. This will allow us to estimate the diagnostic accuracy of tools to within ± 12% (sensitivity) and ± 9% (specificity), assuming accuracy of 80 percent. When identifying characteristics associated with an NDO, assuming we have a binary predictor variable with equal numbers in each category and a baseline risk of 0.33, we will have 80 percent power (alpha=0.05) to identify relative risks of 1.75 or greater.

Patient and Public Involvement

Members of Indigenous communities at each participating site across Queensland have and will continue to be actively engaged at all stages of study development and the research program. Key community stakeholders including community elders, Aboriginal and Torres Strait Islander health workers, Indigenous researchers and people with lived experience as parents of infants/children with cerebral palsy, have been involved in all steps of study design. Consultation and input particularly guided the cultural adaptation and development of culturally safe and sensitive delivery, presentation and feedback of information to families and caregivers including early screening, recruitment and consent processes and key measures to be utilised throughout the program. Consultation and engagement with key stakeholders will continue to be sought throughout program delivery, final analysis and data interpretation.

Strategies targeting key components of cultural safety and sensitivity, consultation and co-design, capacity building and sustainability, are fundamental to the cultural framework that underpins this study and will be led by Indigenous co-investigators. Consumer engagement will be embedded into the study at key screening and outcome timepoints to evaluate parent/caregiver and CHW experience and satisfaction with the screening process and appropriateness and feasibility of assessments.

The final results of the study will be presented in collaborative workshops involving key stakeholders, Aboriginal and Torres Strait Islander community members and personnel at each participating site at the conclusion of the study. Information on the study results will also be reported to all participants as summary data presented to each participating family.

Data Collection Methods

Data collection will commence following consent and enrolment. Extensive perinatal data will be collected from the infant's medical records, including gestational age, birthweight, sex, birth history, neonatal course and maternal risk factors (See **Supplementary** S1: LEAP-CP Medical Checklist: Part 1 – Perinatal data and birth history). Primary caregivers will complete a baseline parent questionnaire that collects detailed socio-demographic information including, maternal and paternal education and employment, social support, family structure and prenatal exposures (See **Supplementary** S1: LEAP-CP Medical Checklist: Part 2- Socio-demographic Information). Caregivers will be given the option to complete this form either independently or during a supported interview with an ILO or Indigenous CHW.

Participants will be screened at two time points, (i) birth to 5 months CA, and (ii) 4 to 9 months CA. Infants can enter the study at any time between birth and 9 months CA, and will commence the relevant screening protocol based on their age at study entry. Outcome measures will be completed at 12 months CA (See Figure 1: LEAP-CP prospective cohort study timeline).

Birth to 5 months CA (Screening stage 1)

Infants recruited prior to 9 weeks CA, will be assessed as an inpatient or outpatient, using the General Movements Assessment, (GMA, writhing period)[48]. The assessment will be recorded by a member of staff who is trained in the procedural guidelines for GMA and uploaded to a secure server. Between 12- and 17-weeks CA infants will be assessed twice using the GMA (fidgety period) via video taken at a clinic appointment or by an application on the caregiver's phone and later uploaded to a secure server. The General Movements smartphone application (Baby Moves;[103]) will be set up on the caregiver's phone by a member of hospital staff or the research team on recruitment to the study. Culturally adapted written/pictorial instructions will be provided to guide caregivers how to video their infant's movements, with support offered by an ILO/CHW. A reminder will be sent via the Baby Moves app to caregivers to ensure videos are recorded at two time-points (ideally at 12- and 14-weeks CA). All GMA videos will be viewed and scored by a minimum of two assessors who are advanced trained by the General Movement Trust and are masked to the participant's identity and medical history. The General Movements Motor Optimality Score (MOS) will be assessed and scored simultaneously using the infant's fidgety GMA videos by the same independent assessors[104].

Assessments at 4 to 9 months CA (Screening stage 2)

The second stage of screening will occur from 4 to 9 months CA. Infants will attend an appointment with a local health care worker where they will be assessed using the HINE, Rapid Neurodevelopmental Assessment (RNDA), Ages and Stages – Aboriginal adaptation (ASQ-TRAK) and clinical assessment of physical features of FASD (photograph with or without direct measurement). The mother or primary caregiver will complete the Depression Anxiety

Stress Scale (DASS-21). Developmental assessments will be administered and scored live by a trained allied health professional, paediatrician, CHW or child health nurse and will be video recorded to allow for independent scoring by a masked assessor. Results from all early screening assessments will be provided to the infant's treating team with parental/caregiver consent. Infants who are rated absent or abnormal fidgety movements on the GMA at 3 months CA and/ or receive a suboptimal HINE score at 4-9 months CA are considered to be at 'high risk' of CP and /or adverse NDO and will be referred to the LEAP-CP intervention trial and linked with local community health services.

Outcomes at 12 months CA

At 12 months CA (± 1 month) all participants will attend an appointment at their local health service. Infants will be assessed by a trained allied health clinician on the HINE, RNDA, ASQ-TRAK, Peabody Developmental Motor Scales – 2nd Edition (PDMS-2), and the cognitive and language scales of the Bayley Scales of Infant Development – 3rd edition (BSID-III). Infants will complete diagnostic specific outcome measures (i) Autism Observation Scale for Infants (AOSI; ASD) and (ii) clinical assessment of physical features of FASD (photograph with or without direct measurement) to determine the presence of symptomology and risk of a later diagnosis of ASD and/or FASD. Assessments will be recorded to allow independent scoring by an assessor masked to the infant's risk of adverse NDOs, medical history and previous assessment findings. A paediatrician, masked to the infant's developmental history, will complete the medical assessment for differential diagnosis from video and photographic (FASD symptomology) assessment (See **Supplementary** S2: LEAP CP: 12-month Medical Assessment – Differential Diagnosis). Caregivers will complete the DASS-21, Infant Toddler Social-Emotional Assessment (ITSEA), Pediatric Evaluation of Disability Inventory - Computer Adaptive Test (PEDI-CAT) and health resource and information questionnaire, either independently or as an interview supported by an ILO or CHW (See **Supplementary** S3: LEAP – CP Medical and Allied Health Resource Form). Child outcomes will be provided to parents/caregivers via written report and results will be forwarded to the infant's treating team with parental/caregiver consent.

MEASURES

Infant Predictor Variables

Prechtl's Qualitative Assessment of General Movements (GMA)

Prechtl's Qualitative Assessment of General Movements (GMA) is a predictive and discriminative tool used to longitudinally observe the quality of early spontaneous movement patterns in infants from birth to 20 weeks CA. The GMA demonstrates high diagnostic accuracy, 97 percent specific and 95-98 percent sensitive, at 3 months CA for detecting infants with a later diagnosis of CP[44-46]. General Movements (GMs) are assessed over specific time periods as either writhing (birth – 9 weeks CA) or fidgety (9-20 weeks CA). Writhing movements are rated as normal, characterised by complex, variable, fluent movements involving the whole body, or abnormal, classified as either poor repertoire, cramped synchronised or chaotic[47,48]. Fidgety movements (FMs) are present from 9 weeks until voluntary, more purposeful movements become predominant[47,48]. Typical (normal) FMs

are defined as small amplitude, multidirectional movements, of the trunk, neck and limbs, of moderate speed, that are continuous in the awake infant, except during periods of crying, fussing and focussed attention[47]. Atypical FMs are classified as either absent or abnormal, referring to either the absence (absent) or exaggeration (abnormal) of typical fidgety movements[47]. While the absence of FMs at 3 months is the best predictor of CP[45], abnormal GMA at writhing age has been associated with later cognitive delays[105], and abnormal fidgety GMA (abnormal or absent) has been associated with early motor delay related to prenatal substance use[36], and is emerging as a potential marker of atypical movement patterns in infants later diagnosed with ASD[35,106]. Assessment of the GMA requires a 3-5-minute video of the infant lying in supine, during periods of active wakefulness, free from distractions. In this study writhing GMA will be completed only if infants are recruited between birth and 4 weeks post term age. Fidgety GMA will occur at two timepoints (ideally between 12- and 17-weeks CA) to give optimal opportunity for FMs to emerge within the 'peak' window[107] and will be scored by at least two advanced trained assessors, masked to the infant's medical and clinical history, to decrease the potential impact of measurement bias.

General Movements Motor Optimality Score (MOS)

The MOS is a more detailed analysis of an infant's fidgety GMA to determine their concurrent motor repertoire at 3-5 months CA by observing postural patterns and movement quality, across five subcategories[104]. The score of each subcategory; quality of fidgety movements, quality of movement patterns, age-adequate movement repertoire, postural patterns and movement character, combine to give a total MOS ranging from 5 to 28[104]. Scores $\geq$25 are optimal and indicative of typical outcomes, scores ranging from 20 to 24 are mildly reduced and MOS <20 requires intervention[57,104]. The presence of specific movement patterns and low scores on the MOS are predictive of a later CP diagnosis and may provide early markers for CP severity, subtype and topography[104,108,109]. Increasing evidence supports the MOS as a prognostic indicator for adverse NDOs (non-CP), and therefore, its function as a transdiagnostic screening tool. Suboptimal MOS scores have been associated with later outcomes of minor neurological dysfunction, language impairments, learning and behavioural difficulties in children without a CP diagnosis[110,111]. Additionally, a monotonous movement character was identified in almost 60% of infants who were prenatally exposed to alcohol and addictive substances[36], has been found in infants with later diagnoses of NDDs (non-CP) including ASD[51] and genetic disorders[104], and, has been linked to cognitive delays at school age in a cohort of high risk infants[112]. The MOS will be assessed and scored concurrently with fidgety GMA, by the same masked, advanced trained assessors.

Hammersmith Infant Neurological Evaluation (HINE)

The HINE is a quantifiable, neurological examination for infants aged 2-24 months CA[113]. It is predictive of suboptimal neurodevelopmental outcomes with 90 percent accuracy in predicting CP in infants aged >18 weeks CA.[44,114]. The HINE is divided into 3 sections, section 1 consists of 26 items that assesses infant neurological function across five domains: cranial nerves, posture, tone, reflexes and movements. Sections 2 and 3 evaluate the infant's motor development and state of behaviour, these sections are not scored[113]. Each item from

section 1 is scored from zero to three, where a score of three is indicative of an optimal item response. Item scores are combined to determine a global optimality score, with a maximum possible score of 78. An infant's global score is compared to age specific optimality scores and cut-offs to determine risk of adverse NDOs[113]. Suboptimal HINE scores (<65, <70) at 6 and 9-12 months respectively are associated with significant delays and/or CP at 2 years[37], with further age specific cut-points (<57 , <60, <63 and <66) at 3, 6, 9 and 12 months respectively, predictive of a later diagnosis of CP[54]. Infants with hemiplegic CP or milder neurological disorders may score above age-specific cut offs[52,54]. Differences observed in item responses between the left and right sides are recorded as asymmetries and are combined to obtain a total asymmetry score. A total of ≥ 5 asymmetries are associated with increased risk of unilateral CP[52]. The HINE is accessible, quick to administer, approximately 5-10 minutes, and has good interobserver reliability, even when performed by less experienced staff[113].

Rapid Neurodevelopmental Assessment (RNDA)

The RNDA is a criterion-based instrument, originally designed to comprehensively assess and identify children 'at risk' of neurodevelopmental impairment (NDI) living in low to middle income countries with limited access to health screening services[80]. The screening tool is intended for use by lay health workers and has been successfully integrated into Aboriginal Health clinics at Gidgee Healing in Mt Isa, Queensland[115,116]. The instrument assesses the functional status of children aged 0-9 years to determine the presence and severity of NDIs across multiple domains[80,117,118]. Infants aged 1-24 months CA are assessed across eight domains: gross motor, fine motor, vision, hearing, speech, cognition, behaviour and seizures. Each item is scored on a 4-point scale, as normal = 0, mild= 0.5, moderate=1 or severe=2 impairment. The sum of item scores are used to determine the presence and degree of impairment for each domain[119]. The RNDA has been validated in infants ≤2 years CA to determine the presence of NDI vs no NDI[80] and demonstrates moderate to high agreement with the Bayley Scales of Infant Development – second edition and BSID-III for identifying infants aged <12 months CA with and without NDIs[80,120]. The RNDA has good face validity, evident in its acceptability by caregivers, clinicians and infants, and has been culturally adapted for use in other countries[80,120]. The RNDA has high interrater reliability among medical professionals across the domains of gross motor (k=1.00), behaviour (k=1.00), fine motor (k=0.93) and seizures (k=0.91), with moderate agreement for cognition (k=0.80), hearing (k=0.78) and speech (0.63)[80]. A similar level of agreement was also demonstrated between local community workers and trained health professionals across cognition, speech, behaviour, gross and fine motor domains[120]. Administration time for the RNDA is between 30-45 minutes and must be completed by a trained clinician or health worker[80].

Ages and Stages Questionnaire, Australian Aboriginal adaptation (ASQ- TRAK)

The ASQ-TRAK (adapted from the Ages and Stages Questionnaire 3rd edition;[79]) is the only developmental screening tool that has been adapted and validated specifically for use in an Australian Indigenous context[121,122]. The ASQ-TRAK demonstrates acceptable accuracy, sensitivity (71 percent), specificity (92 percent), for detecting developmental concerns in Indigenous children, and, has demonstrated concurrent validity with the BSID-III, with moderate correlation between corresponding domain scores on both tools[121]. The ASQ-

TRAK consists of interview-based questionnaires available for children aged 2, 6, 12, 18, 24, 36 and 48 months, assessing outcomes across five areas; communication, gross motor, fine motor, problem solving, personal-social[123]. The screening tool contains the same items and scoring as the ASQ-3 but is based on a caregiver interview, with opportunity for the child to demonstrate skills. Culturally relevant adaptations to the ASQ-3 include, translation into local language and item modifications to ensure cultural relevance[123]. Individual items are assessed as "yes", "sometimes" or "not yet" to ascertain a score of 10, 5 or 0 respectively. Individual, domain specific, item scores are combined to determine the total domain score (maximum = 60). Scores are compared to domain specific cut-offs to determine risk of developmental delay, with further assessment recommended for infants who score below the cut off, or 'at risk', for any domain[122]. The ASQ-TRAK has proven face validity and was determined to be culturally relevant and acceptable by Aboriginal health care workers and parents[123,124]. The screener takes 30-60 minutes to complete and can be administered by trained health care workers[121].

Outcome Measures

1. Infant

Outcomes will be assessed at 12 months CA (± 2 weeks) by a trained allied health clinician and videoed for scoring by a researcher masked to perinatal data and earlier assessment data points.

Peabody Developmental Motor Scales second edition (PDMS-2)

Infant primary motor outcomes at 12 months CA will be assessed using the PDMS-2, a standardised, norm-referenced measure used to evaluate the gross and fine motor development of children aged birth to 6 years[125]. The gross motor component is comprised of four subtests: reflexes, stationary, locomotion and object manipulation. Two subtests, grasping and visual-motor integration, form the fine motor component[125]. Individual items are allocated a score from zero to two based on performance, 0 (unable to perform), 1 (partial performance) or 2 (correct performance). Subtest raw scores are used to determine motor outcomes and ascertain the presence and severity of motor delay. The PDMS-2 has demonstrated predictive validity, sensitivity (92 percent), to identify abnormal development at 18 months in preterm infants assessed at 8 months[126]. The assessment has concurrent validity with both the BSID-III[127] and the Gross Motor Functional Measure[128]. The PDMS-2 is responsive to change in a population of infants[129] and toddlers with CP[130]. The assessment takes 45-60 minutes to complete, with formal training not required for the administration and scoring of the PDMS-2.

Bayley Scales of Infant Development – 3rd edition (BSID-III)

The BSID-III is the gold standard, norm-referenced assessment for measuring the development of infants and toddlers, aged 1–42 months, to determine infant cognitive and communication outcomes at 12 months CA. The BSID-III comprises five scales, cognitive, language, motor, social-emotional and adaptive behaviour. Items are administered in a standardised procedure and scored as either credit=1 or no credit=0. A composite score of >2 SD below the mean on any scale is indicative of delay and supports the need for intervention[131]. In this study we

will use the BSID-III cognitive and language scales to assess infant outcomes at 12 months CA. The BSID-III (cognitive and language scales) have demonstrated predictive validity for outcomes on the Weschler Preschool and Primary Scale of Intelligence –III at 4 years of age[132]. Internal consistency reliability and test re-test reliability were determined for the composite and subtest scores on the Bayley III cognitive and language scales across all ages, with higher reliability demonstrated in age groups >6 months of age[131]. The BSID-III low motor/low vision version will be used to improve validity when assessing children with mild to moderate motor and/or vision impairment[133]. While the Bayley IV is now available[134] the Bayley III will be used in this study to compare this Indigenous cohort to other non-Indigenous Australian cohorts[135]. A trained professional is required to administer the assessment, average time taken to complete varies with age and ranges from approximately 50 – 90mins[131,136].

The Pediatric Evaluation of Disability Inventory-computer adaptive test (PEDI-CAT):

Developmental outcomes in self-care, mobility and social function will be assessed at 12 months CA using the PEDI-CAT, a standardised, norm-referenced assessment of independence in self-care[137]. The PEDI-CAT has been designed for use from birth to 21 years of age and has been Rasch analysed in children with disability and typical development[137]. The instrument measures functional outcomes across four domains, daily activities, the ability to perform living skills, mobility, the ability to move around the home and in the community, and, social/cognitive the ability to participate and effectively engage in social situations. Responsibility, the fourth domain, will not be assessed in this study[137]. The tool is administered via a web-based application (Q-global), allowing parents/caregivers to self-report their child's independence on each domain. The PEDI-CAT uses an item bank which automatically lowers the number of test items dependent on how the child is scoring[137,138]. Items are scored on a 4-point difficulty scale with responses ranging from unable to easy. Normative scores are reported as a T-score and an age percentile range ($<5^{th}$, 5^{th} – 25^{th}). The PEDI-CAT has good discriminant validity in CP populations, between children with and without disability, and, demonstrates concurrent validity with the Wee-FIM in children with brain injury and developmental disabilities[139-141]. The PEDI-CAT is frequently used as an assessment to determine entry and allocation of resources for children entering the Australian National Disability Insurance Scheme (NDIS)[142]. The test is valid, reliable and responsive in this population, takes 10-15 minutes to complete, and test administration requires no formal training[141,143].

Infant Toddler Social and Emotional Assessment (ITSEA)

The ITSEA is a 168 item, parent-report questionnaire designed to evaluate social-emotional and behavioural competencies and difficulties in infants aged 12 months to 3 years old[144]. The instrument measures items across four behavioural domains; externalising, internalising, dysregulation and competencies. Items are scored on a 3-point (0-2) scale, not true/rarely (0), somewhat true/sometimes (1), and, very true often (2)[144]. The ITESA is discriminative between high and low risk infants with social-emotional difficulties at 12 months of age[145], and demonstrates strong test-re test reliability (α=.75-.91)[146].

2. Diagnostic assessments

At 12 months CA infants will be assessed by a paediatrician who will complete a medical assessment for differential diagnosis (**Supplementary** S2: LEAP-CP 12-month Medical Assessment) including documenting the presence of ASD and FASD symptomology. Functional severity, motor type and distribution of CP will be ascertained for infants who have a confirmed or high-risk diagnosis of CP.

Diagnosis of Cerebral Palsy

Confirmed or high risk CP will be diagnosed according to published guidelines[147-149], based on clinical history (LEAP-CP Medical checklist) and videoed HINE and PDMS-2 assessments.

Motor type and distribution

Motor type will be classified as spastic, dystonic, ataxic, choreoathetosis, mixed CP or unclassifiable according to Surveillance of Cerebral Palsy in Europe (SPCE) guidelines [148]. Motor distribution will be classified by number of limbs impaired and uni- or bi-lateral distribution by an independent assessor.

Functional severity

The Gross Motor Functional Classification System (GMFCS) has validity, reliability and stability for the classification and prediction of motor function of children with CP aged 2-12 years[150-152]. The GMFCS extended and revised version, 0-2 year descriptors, will be used to classify the gross motor abilities of infants at 12 months CA[153]. The GMFCS has been correlated with CP motor type and distribution[154].

The Mini Manual Abilities Classification Scale (MACS) is used to classify hand function and abilities in children aged 0-4 years and is the gold standard for classifying infant's ability to handle objects in daily activities[155]. An independent assessor will use videos to observe and classify children in one of five functional categories for each scale.

ASD symptomology

The Autism Observation Scale for Infants (AOSI) will be used to measure ASD symptomology at 12 months CA [156]. The AOSI, a semi-structured observational tool, was designed to assess the presence and emergence of specific ASD related behaviours in infants aged 6-18 months[71,156]. The experimenter led tool assesses 18 items, individual item scores range from 0-3 and are combined to obtain a total score, with higher scores indicating elevated risk of ASD behaviours[71]. The presence of 7 or more risk markers at 12 months was 52% sensitive and 74% specific for an ASD diagnosis at 3 years[75]. The AOSI differentiates between high-risk and low-risk infants at 12-18 months[73,75,76,157]. Inter-rater reliability for individual items and total scores is excellent (0.92 and 0.93, respectively) at 12 months and test -retest reliability is acceptable[71].

FASD symptomology

Assessment of PAE

The Alcohol Use Disorders Identification Test- Consumption (AUDIT-C) will be used to ascertain the potential level of fetal risk associated with maternal alcohol use during pregnancy (pre- and post-pregnancy recognition). The validated, sex-specific version of the instrument

comprises three questions as a standardised method of assessing maternal alcohol consumption [158,159]. An AUDIT-C score of ≥5 or a reported consumption of 5 or more standard drinks on one occasion is associated with increased risk of FASD[88,159].

Sentinel Facial features

Clinical assessment of facial features will be completed via direct measurement (where possible) and/or assessed from a photograph, analysed using the University of Washington facial analysis software[160]. Smooth philtrum and thin upper lip will be assessed using the University of Washington Caucasian or African American (depending on what is individually appropriate) lip-philtrum guide (1 or 2), where a rank of 4 or 5 meets criteria for FASD sentinel facial features. The Scandinavian (Stromland) chart will be utilised to measure palpebral fissure length where a result of ≥2 SD below the mean (<3rd percentile) is significant [88,161]. Standard frontal and oblique facial photographs will be analysed using the FAS Facial Photographic Analysis Software for facial dysmorphology assessment[160].

Severe Neurodevelopmental Impairment

Assessment of impairment will target five of the ten neurodevelopmental domains that reflect known areas of brain function affected by PAE[88]. Infant's neurological, motor, cognitive, language and adaptive and social skills will be assessed using standardized outcome measures at 12 months CA. Severe impairment will be defined as score of ≥2 SD below the mean, or equivalent, on the HINE (neurological), PDMS-2 (motor), Bayley III (cognitive and language scales), PEDI-CAT (adaptive/social) and ITSEA (behaviour)[88]. Infants with a head circumference less than <3rd centile and/or abnormal brain imaging including structural brain abnormalities will also be considered as criteria for severe brain structure/neurological impairment[88]. Presence and severity of impairment will be determined by assessors blinded to the infant's clinical history and predictor assessment outcomes.

Special considerations for infants

In children under 6 years of age with all 3 sentinel facial features and microcephaly a diagnosis of FASD with 3 Sentinel Facial Features can be made, regardless of confirmed PAE and in the absence of severe neurodevelopment impairment in 3 domains. In the absence of microcephaly, children under 6 years of age with all 3 sentinel facial features are considered 'at risk of FASD', whether PAE is confirmed or unknown[88].

3. Parent/Caregiver

Depression Anxiety Stress Scale (DASS-21)

Parent or primary caregiver mental health status will be assessed at two time-points (screening stage 2 and infant 12-month outcomes) using the DASS-21, a 21-item, self-reported tool designed to measure the presence of the negative emotional states of depression, anxiety and stress[162]. Individual items assess the presence of symptoms across 3 subscales (depression, anxiety and stress). Participants use a 4-point scale to reflect and rate the extent to which they have experienced each symptom over the past week. Item scores are combined to determine the severity; normal, mild, moderate, severe or extremely severe, for each emotional state[162]. The DASS-21 has demonstrated concurrent validity with the Beck depression and anxiety inventories[163,164] and has been utilised in a population of Indigenous mothers to assess maternal emotional wellbeing[165].

Co-Variates and Descriptive measures

Perinatal Data

An extensive record of antenatal, birth history and the neonatal course will be collected at the time of infant enrolment from medical records (See **Supplementary** S1: LEAP-CP Medical checklist). Data collected will include:

i. Demographic data including gestational age, birth weight, sex and multiple birth status.
ii. Perinatal events that signify complications during labour and delivery, indicating increased risk of adverse NDO.
iii. Neonatal medical complications associated with adverse NDOs including early brain injury, infection, necrotising enterocolitis, respiratory distress, bronchopulmonary dysplasia, postnatal infant steroid therapy, neonatal surgery, retinopathy of prematurity, prolonged use of oxygen and feeding status at discharge.
iv. Maternal risk factors that may impact neonatal outcomes, including, antenatal medical complications and treatment, medical conditions (diabetes mellitus, epilepsy), antenatal substance use, mental health status and family history of adverse NDOs.

Clinical neuroimaging

Cranial Ultrasound (CUS) and MRI assessment findings will be collected and retrieved from Hospital records. Abnormal MRI, including white matter injury, cortical and grey matter lesions and brain maldevelopments may be indicative of neuroanatomy abnormalities predictive of adverse NDOs[45]. MRI findings will be utilised in the diagnostic process for CP and symptomology of FASD.

Demographic data

Demographic data will be collected at two time points:
The LEAP-CP Medical Checklist: Part 2 (**Supplementary** S1), completed at study enrolment, details information regarding family structure and supports, primary language spoken at home, maternal and paternal education, and employment status. The Social Risk Index (SRI) and the AUDIT-C questionnaire will be embedded into this document to ascertain level of family social risk and infant PAE[159,166].
The LEAP-CP Medical Resource form (**Supplementary** S3), completed at or prior to the 12-month CA appointment, to provide information regarding their child's development, access to services and eligibility and/or access to NDIS funding.

Social Risk Index (SRI)

The 12-point SRI measures six aspects of social status; family structure, language spoken at home, maternal age at birth and primary caregiver education, occupation and income. Risk items are scored from 0-2, with a lower score associated with lower risk. Overall family risk scores will be classified as lower (≤1) or higher social risk (>2) [167,168]

DATA MANAGEMENT AND ANALYSIS PLAN

All data will be entered into a REDcap database by ID number (re-identifiable). Data analysis will be carried out using Stata v16.0[169] statistical software package . Predictor and outcome variables will be identified as continuous, categorical or binary. Analysis will explore means,

variability and distributions of continuous variables and the rate of occurrence and distribution of binary variables. Infants will be categorised at 12 months CA as at risk of specific NDD, (i) CP, (ii) ASD, (iii) FASD (as defined by the presence of disorder specific symptomology) and/or (iv) adverse NDO (non-specific, defined as >2SD below the mean or equivalent on 1 developmental domain and/ or >1SD below mean in ≥2 domains), or (v) typically developing (≤1SD below the mean or equivalent on all developmental domains) or borderline (mild delay; between 1 and 2SD below the mean on 1 domain). Logistic regression analysis (binary outcomes), linear regression (continuous outcomes) and multinomial logistic regression (categorical outcomes) will be used to determine any associations between predictor and outcome variables. Diagnostic statistics, including sensitivity, specificity, positive and negative predictive values and accuracy of the predictive assessments (GMA, MOS, HINE, RNDA and ASQ-TRAK) will be determined with 95% confidence intervals based on an outcome of 'at risk' of specific NDD, (i) CP, (ii) ASD, (iii) FASD and/or (iv) adverse NDO (non-specific) at 12 months CA. Perinatal variables, social and environmental data, caregiver mental health outcomes (DASS-21) and clinical neuroimaging will be utilised as descriptive measures and covariates in regression models.

DISCUSSION

Results of this study will inform service delivery of follow-up pathways for Indigenous infants at risk of adverse NDOs and their families. Our findings will inform culturally sensitive practice and enable clinicians to select both clinically meaningful and culturally appropriate tools to identify Indigenous infants at high risk of adverse NDOs at an earlier age. Early detection will fast track families to access early intervention services for Indigenous infants and families and enable early referral to the targeted motor and cognitive training in the LEAP-CP clinical trial (trial registration: ACTRN12619000969167) and or mainstream allied health services to promote optimal outcomes.

Strengths and Limitations

Infants will be recruited early to establish discharge pathways and a follow up plan, with local services. Engagement, and established connections with local health services will enable locally trained Indigenous CHWs to assist in the screening process for infants and families living remotely, with support provided via telehealth as required. Culturally adapted resources, developed in partnership with Indigenous co-investigators and consumers, will be utilised to facilitate safe and sensitive communication and practices throughout the screening and diagnostic process for infants and families. This study aims to foster local Indigenous workforce capacity through skill development and training opportunities and build upon current models of care to enable feasible and sustainable early detection programs for 'at risk' Indigenous infants. Assisting existing services to implement culturally appropriate screening programs will ensure these strategies and pathways can be embedded into regular service delivery models at the conclusion of the study.

The cultural, geographical and language barriers within this study present potential limitations and confounding factors. The ability to follow up Indigenous infants who live remotely may be a challenge, as remote locality is a reality for many QLD Indigenous communities, which limits ability to access health services. Infants who are identified as low risk following

screening may be less likely to attend their 12-month CA follow up appointment, impacting study retention. In addition, challenges in recruitment and retention of health professionals in remote communities may further limit physical access to these services.

Ethics and Dissemination of findings

Ethics committee approvals were obtained from the appropriate Indigenous ethics/governance committees (see acknowledgements). There are no known health or safety risks associated with participation in any aspect of the described study. Cultural adaptations will be made to all resources and throughout the study families will be given the option to verbally discuss any questions or concerns with an ILO or CHW to ensure comprehension of concepts, cultural and language barriers are addressed. Families can withdraw their child from the study at any time without explanation, without any penalty from staff at the treating or referring hospital or health service, or any effect on their child's care. Data collected in this study will be securely stored in a coded re-identifiable form (by ID number at the University of QLD). Summary data of outcome measures will be shared with the treating clinician and/or team with the parent/caregiver's permission.

Findings of this study will be of interest to medical, allied health and community health workers, working with Indigenous infants and families in urban, rural and remote communities. Findings will be disseminated via peer-reviewed publications, conference presentations, clinical practice guidelines outlining culturally appropriate screening tools and sensitively communicating a diagnosis and resources including culturally adapted factsheets.

ABBREVIATIONS

AOSI	Autism Observation Schedule in Infants
ASD	Autism Spectrum Disorder
ASQ-TRAK	Ages and Stages – Aboriginal adaptation
AUDIT-C	Alcohol Use Disorders Identification Test- Consumption
Baby Moves	General Movements smartphone application
BSID-III	Bayley Scales of Infant and Toddler Development – Third Edition
CA	Corrected age
CHW	Community Health Worker
CP	Cerebral Palsy
CUS	Cranial Ultrasound
DASS-21	Depression Anxiety Stress Scale
FASD	Fetal Alcohol Spectrum Disorder
GMA	General Movements Assessment
HHS	Hospital and Health services
HINE	Hammersmith Infant Neurological Examination
ILO	Indigenous Liaison Officer
ITSEA	Infant Toddler Social-Emotional Assessment
LBW	Low Birth Weight
MRI	Magnetic Resonance Imaging
NDD	Neurodevelopmental Disorder
NDO	Neurodevelopmental Outcome
NDI	Neurodevelopmental Impairment
NICU	Neonatal Intensive Care Unit
PAE	Prenatal Alcohol Exposure
PNN	Post neonatal
PDMS-2	Peabody Developmental Motor Scales – 2nd Edition
PEDI-CAT	Pediatric Evaluation of Disability Inventory - Computer Adaptive Test
RNDA	Rapid Neurodevelopmental Assessment
SCN	Special Care Nursery
SGA	Small for Gestational Age
SRI	Social Risk Index

COMPETING INTERESTS

The authors declare they have no competing interests.

AUTHOR'S CONTRIBUTIONS

Ms Luke had substantial input into study design, ethics applications and was the lead author for the protocol manuscript. she will take a lead role in the recruitment, data collection and analysis of the study.

Dr Benfer had substantial input to the study design including methods and key outcome measures, ethics applications and engagement with key community leaders. She provided feedback and revision throughout manuscript development.

Ms Mick-Ramsamy lead the cultural engagement with key community stakeholders for the study. She lead the cultural adaptations and contributed to the cultural voice of the manuscript. She provided feedback and revision throughout manuscript development.

Dr Ware lead the statistical design and analysis component of the paper and contributed to the study design in particular sample size and statistical analysis. He provided feedback and revision throughout manuscript development.

Dr Reid contributed in particular to the FASD diagnostic and symptomology design and component of the manuscript. She also provided key insight to working with First Nations communities. She provided feedback and revision throughout manuscript development.

Dr Bos provided expert consultation regarding the use of the general movements assessment in particular the more detailed analysis using the motor optimality score. He provided key additions to the manuscript and study design and will continue to work as a consultant for the study. He provided feedback and revision throughout manuscript development.

Dr Bosanquet is part of Ms Luke's PhD advisory team, she provided key input into the study design and methodology in the context of regional Queensland. Her contributions regarding rehabilitation medicine were integral to the manuscript development. She provided feedback and revision throughout manuscript development.

Prof Boyd is Ms Luke's primary advisor and provided key input into the study design. She provided high level feedback and revision throughout the manuscript development and signed off on final revisions. Ms Boyd led the engagement with Leeann Mick-Ramsamy with First Nations communities and was integral to all parts of the study including ethics applications.

COLLABORATOR CONTRIBUTIONS

Collaborators who have provided assistance with patient care and data collection: Apunipima Cape York Health Council, Gidgee Healing, Gurriny Yealamucka Health Service Aboriginal Corporation, Townsville HHS, Cairns and Hinterland HHS, Children's Health Queensland HHS

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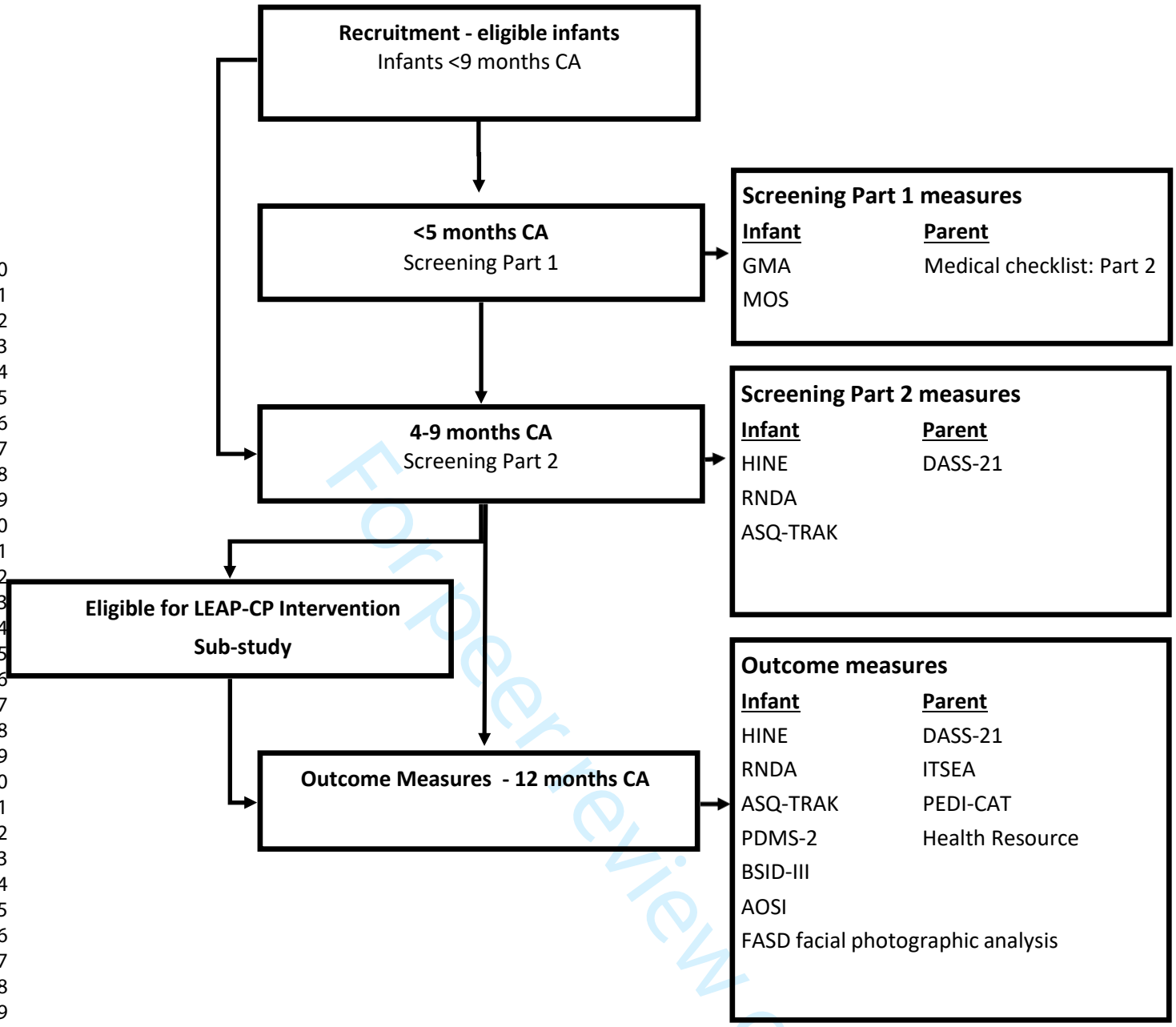

Figure 1: LEAP-CP prospective cohort study timeline

Key: GMA= Prechtl's General Movements Assessment, MOS= General Movements Assessment Motor Optimality Score, HINE= Hammersmith Infant Neurological Examination, RNDA= Rapid Neurodevelopmental Assessment, ASQ-TRAK= Ages and Stages Questionnaire-Aboriginal Adaptation, PMDS-2= Peabody Developmental Motor Scales 2nd Edition, BSID-III= Bayley Scales of Infant Development 3rd Edition, PEDI-CAT= Pediatric Evaluation of Disability Inventory - computer adaptive test, AOSI= Autism Observation Schedule in Infants, FASD facial photographic analysis, DASS-21= Depression Anxiety Stress Scale, ITSEA= Infant Toddler Social Emotional Assessment

Supplementary Information

S1: LEAP-CP Medical checklist: Part 1 and 2

Study ID: ☐☐☐ **Date:** ☐☐/☐☐/☐☐☐☐
Form completed by: **Interviewer initials:** ☐☐

Part 1: Perinatal data and Birth History – collected from Medical record

Infant details

Estimated date of delivery	
Date of birth	
Gestational age at birth (weeks.days)	
Maternal age at birth	
Gender	O Male O Female O Indeterminate
Multiple Births	O Singleton O Twin O Triplet O Surviving twin from multiple (eg singleton birth from triplet pregnancy, sibling died in utero or at birth)
Order of birth for multiples	
Birthweight (grams)	
Apgar at 1 minute	
Apgar at 5 minutes	
Resuscitation	O Nil (includes suction & O2 therapy) O Minor (bag and mask, CPAP or Hi-flow) O Major (intubation, CPR, adrenaline) O Resuscitation data not recorded

Infant complications

Respiratory (tick all that apply) Other respiratory issue please specify	O No (includes suppl O2 for <4 hrs) O Requiring ongoing ventilation or CPAP O Pneumothorax O Pneumonia O Other
Chronic lung disease (O2 and or ventilatory requirement at 36 weeks corrected age)	O Yes O No
Hypxoic Ischemic Encephalopathy (HIE)	O Yes O No
Sarnat stage or severity of HIE	O Stage 1 (mild) O Stage 2 (moderate) O Stage 3 (severe)
Received cooling	O Yes O No
Patent ductus arteriosus (PDA)	O No O Yes O Not documented
If yes to PDA, tick all that apply	O No treatment O Diuretics O Fluid restriction O Indomethacin/ibuprofen/paracetamol

	O Surgery
NEC	O No O Suspected (clinical signs, Xrays normal, nil by mouth &/antibiotics <5 days) O Definite (Xray changes, ≥5 days nil by mouth &/or triple antibiotics &/or surgery)
Seizures Aetiology if known	O Yes O No
Surgery	O Yes O No
Please specify what surgery (tick all that apply) Other surgery, please specify	O Bowel resection O Inguinal hernia repair O Tracheostomy O PDA ligation O Rickham's reservoir O VP shunt O other
Jaundice requiring exchange transfusion	O Yes O No
Major malformation or genetic syndrome Please specify	O Yes O No
Retinopathy of Prematurity (ROP)	O No O Yes, no intervention required O Yes, received laser therapy O Yes, received Avastin (brand name for Bevacizumab) O Not examined
Left eye: Max stage of ROP as recorded by ophthalmologist	
Right eye: Max stage of ROP as recorded by ophthalmologist	
Hearing Screen result Referred hearing result	O Pass O Referred for further examination O Not examined

Cranial and MRI findings Ultrasound findings (most severe reported)

IVH Maximum IVH grade Left Maximum IVH grade Right	O Yes O No
Cystic PVL	O Yes O No
Please specify any other abnormal neuroimaging findings	
Age at time of CUS/MRI	
Where was the CUS/MRI completed	

Discharge details

LOS in hospital (days) NICU SCN Transfered to other hospital	
Discharged home on Oxygen	O Yes O No
Was the infant receiving any tube feeding on discharge home?	O Yes O No

Developmental History

Complications since birth (please tick all that apply) Other, please specify	O CNS infection (eg meningitis/ encephalitis) O Head injury O Near drowning O Non-accidental injury O Tumour O CVA O Cerebral malformation O Other

Maternal details

Maternal age at delivery	
Mode of delivery	O Vaginal O Caesarean – in labour O Caesarean – not in labour O Not documented
Specify Caesarean section	O Elective O Emergency
Did the infant have foetal growth restriction?	O Yes O No
Did the mother have any of the following medical conditions during this pregnancy?	O None O Pre-eclampsia O Essential hypertension O Thrombophilia O Diabetes - specify O Epilepsy O Respiratory - specify O Renal disease - specify O Cardiac disease - specify O Pulmonary - specify O Red cell isoimmunisation O Autoimmune disease - specify O Psychiatric (diagnosed) - specify O Substance use - specify O Other
Diabetes (please specify)	O Gestational O Type 1 diabetes O Type 2 diabetes
Respiratory (please specify)	

Renal disease (please specify)	
Cardiac disease (please specify)	
Pulmonary (please specify)	
Autoimmune (please specify)	
Psychiatric (please specify)	
Substance use (please specify)	
Other (please specify)	
Antepartum haemorrhage (bleeding after 20 weeks gestation)? If Yes, specify at what gestation	O Yes O No
Did the mother receive corticosteroids (to enhance foetal lung maturation)?	O Yes O No O Not documented
Antenatal corticosteroids (number of completed courses; 2 doses = 1 course)	O None O Incomplete (1 dose only) O 1 course O 2 courses O 3 courses O Information not documented
Did the mother receive any intravenous magnesium sulphate	O No O Yes O Not documented
Duration of ruptured membranes	O N/A or no data available O <24 hours O ≥24 hours
Were antibiotics given?	O No O Yes O Not documented
Did any of the following intra &/or post-partum complications occur? Other, please specify	O None O Intra-partum fever (in mother) O Preterm labour O Meconium O Breech O Shoulder dystocia O Delayed cry (>5 minutes after birth) O Lethargy or seizures within 72 hours of birth O Cord around neck O Other
Antenatal care Number of visits	O Yes O No

Medications

During the last 6 months has your child had medications for…

1. Epilepsy	O Yes O No
A. Which medication	
Frequency (per day)	☐☐
Dosage (per day)	☐☐
Duration (length of treatment)	
Any adverse effects?	O Yes O No
B. Which medication	
Frequency (per day)	☐☐
Dosage (per day)	☐☐
Duration (length of treatment)	
Any adverse effects?	O Yes O No
C. Which medication	
Frequency (per day)	☐☐
Dosage (per day)	☐☐
Duration (length of treatment)	
Any adverse effects?	O Yes O No

2. Saliva control	O Yes O No
A. Which medication	
Frequency (per day)	☐☐
Dosage (per day)	☐☐
Duration (length of treatment)	
Any adverse effects?	O Yes O No
B. Which medication	
Frequency (per day)	☐☐
Dosage (per day)	☐☐
Duration (length of treatment)	
Any adverse effects?	O Yes O No

3. Other	O Yes O No
A. Which medication	
Frequency (per day)	☐☐
Dosage (per day)	☐☐
Duration (length of treatment)	
Any adverse effects?	O Yes O No
B. Which medication	
Frequency (per day)	☐☐
Dosage (per day)	☐☐
Duration (length of treatment)	
Any adverse effects?	O Yes O No

Co-morbidities

	Parent question (based on 10Q Screen)*	**Formal assessment**
Physical	Does your child have any serious delay in sitting, standing or walking? O Yes O No Does your child have difficulty walking or	

	using arms or does he/ she have weakness in the arms/ legs? O Yes O No	
Epilepsy/ infantile seizures (date of onset) and seizure type	Does your child sometimes have fits, become rigid, or lose consciousness? O Yes O No	Date of onset (from above): Type of seizure (from above): Defined by 2 unprovoked seizures excluding febrile or neonatal seizures O Generalised or partial O Generalised – sudden onset of seizures that compromises responsiveness and affects the whole body O Partial – seizures have focality therefore symptoms reflect onset in 1 part of the brain
Visual impairment	Compared with other children, does your child have difficulty seeing, either in the daytime or at night? O Yes O No	O No O Diagnosed impaired O Suspected impaired O Unsure
Hearing impairment	Does your child appear to have difficulty hearing? O Yes O No	O No O Diagnosed impaired O Suspected impaired O Unsure
Intellectual impairment	Does your child learn to do things like other children his/ her age? O Yes O No Compared with other children of his/ her age, does your child appear in any way mentally backward, dull or slow? O Yes O No	O No O Diagnosed impaired O Suspected impaired O Unsure
Communication impairment	When you tell your child to do something, does he/ she seem to understand what you are saying? O Yes O No Does your child speak at all? O Yes O No Can your child name at least one object? O Yes O No	O No O Diagnosed impaired O Suspected impaired O Unsure

*10 Question Screen is a standardised parent-reported measure. Please ask these questions verbatim.

Part 2: Socio-demographic information

Household Characteristics

Family pedigree (3 generations) * Note this is not completed if biological caregiver is not involved and information is not recorded in the infant's medical record.	Any evidence of illness in the family; any problems with development or intellect; presence of motor disorder, congenital deformity, decreased motor function over time, in-utero/death, disease; cousin marriage, sudden/ unexplained death				
Family structure	2 caregivers (nuclear)	Separated parents dual custody	Cared for by other intact family	Single caregiver	Other
Birth order (of blood siblings	First born	Second born	Third born	Fourth born	Other (specify)
Child lives with	Nuclear family	Extended family	Step family	Kinship care	Foster care
Family members in the house (number)				Adult men	
				Adult women	
				Children <18 years	
Other relatives living close by	Yes / no				
Who regularly provides care for the child (multiple times per week)? (select as many as apply, and provide their details) Other (specify):	**Relationship to child:** Age: Highest education: Occupation: Frequency of care:	**Relationship to child:** Age: Highest education: Occupation: Frequency of care:	**Relationship to child:** Age: Highest education: Occupation: Frequency of care:	**Relationship to child:** Age: Highest education: Occupation: Frequency of care:	**Relationship to child:** Age: Highest education: Occupation: Frequency of care
Does the infant's biological mother/ father identify as	Aboriginal	Torres Strait Islander			
Primary language(s) spoken at home	English only Specify language(s):	Some English	No English		
Where family traditionally from?					
Current postcode					
Distance to town (corner store)	☐☐☐ minutes (in car)				

Employment

Who are the main earners/ workers in the family?	Grandfather	Grandmother	Father	Uncle	Mother	Other
Main earners' occupation/s						
Main earner's employment	Fulltime/ secure	Part-time/ casual	Unemployed/ pension		Fly in fly out	
Does ill-health often prevent them from working?	Y		N		NA	

Alcohol use in early pregnancy (AUDIT-C)*

Was the pregnancy planned or unplanned?	O Planned O Unplanned O Unknown
At what gestation did the mother realise she was pregnant?	Weeks O Unknown
Did the birth mother drink alcohol before the pregnancy was confirmed?	O No O Yes O Unknown
Did the birth mother modify her drinking behaviour on confirmation of pregnancy?	O Yes O No O Unknown
During which trimesters was alcohol consumed, tick all that apply	O None O 1st O 2nd O 3rd O Unknown
1. How often did the birth mother have a drink containing alcohol during this pregnancy?	O Unknown O Never (skip Qn 2 & 3) O monthly or less O 2-4 times a month O 2-3 times a week O 4 or more times a week
2. How many standard drinks did the birth mother have on a typical day when she was drinking this pregnancy?	O Unknown O 1 or 2 O 3 or 4 O 5 or 6 O 7 to 9 O 10 or more
3. How often did the birth mother have 5 or more standard drinks on one occasion during this pregnancy?	O Unknown O Never O Less than monthly O Monthly O Weekly O Daily or almost daily

* Note this is not completed if biological caregiver is not involved and information is not recorded in the infant's medical record.

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S2: LEAP- CP (Learning through Everyday Activities with Parents) _ 12-Month Medical Assessment- Differential Diagnosis

Study ID: ☐☐☐ **Date:** ☐☐/☐☐/☐☐☐☐

Completed by:

Child's name	
Corrected Age at assessment	
Weight	kg / percentile
Height	cm / percentile
Head Circumference	cm / percentile

Visual impairment (without correction, on both eyes)	Not assessed =0	Right (R=), Left (L=)
	Normal/No visual impairment =1	
	Squint =2	
	Impaired =3	
	Severely impaired (blind or no useful vision) =4	
Hearing impairment (before correction, on the better ear)	Not assessed =0	
	Normal =1	
	Impaired =2	
	Severely impaired (hearing loss > 70 dB) =3	

General Observation:	No abnormality =0	Abnormality=1
Face	0	1
dysmorphism	0	1
general nutritional state	0	1
Body proportions	0	1
Muscle bulk	0	1
symmetry	0	1
tongue fasciculation	0	1
excessive drooling	0	1
other	0	1

Gait:	Non ambulant = 0	**Comments:**
	Age appropriate = 1	
	Toe walking = 2	
	Asymmetrical gait = 3	

CEREBRAL PALSY

Motor type	**Primary**	**Secondary**
	Spastic =1	Spastic =1
	dyskinetic- dystonic =2	dyskinetic- dystonic =2
	dyskinetic- choreoathetotic =3	dyskinetic- choreoathetotic =3
	Hypotonic =4	Hypotonic =4
	Ataxic =5	Ataxic =5
Distribution	Bilateral =1 / unilateral =2	Bilateral =1 / unilateral =2
	No of limbs 1 / 2 / 3 / 4	No of limbs 1 / 2 / 3 / 4

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Neurological Signs:

Tone:	Left				Right			
Upper Limbs	Not tested = 0	Normal =1	Hypotonic =2	Hypertonic =3	Not tested = 0	Normal =1	Hypotonic =2	Hypertonic =3
Lower limbs	Not tested = 0	Normal =1	Hypotonic =2	Hypertonic =3	Not tested = 0	Normal =1	Hypotonic =2	Hypertonic =3

Tendon Reflexes:	Left	Right
Upper Limbs	Not tested =0 Present/Normal =1 Absent =2 Depressed =3 Brisk =4 Hyperreflexic/Very Brisk =5	Not tested =0 Present/Normal =1 Absent =2 Depressed =3 Brisk =4 Hyperreflexic/Very Brisk =5
Lower limbs	Not tested =0 Present/Normal =1 Absent =2 Depressed =3 Brisk =4 Hyperreflexic/Very Brisk =5	Not tested =0 Present/Normal =1 Absent =2 Depressed =3 Brisk =4 Hyperreflexic/Very Brisk =5

Clonus:						
Upper Limbs	Not tested = 0	Absent =1	Present =2	Not tested = 0	Absent =1	Present =2
Lower limbs	Not tested = 0	Absent =1	Present =2	Not tested = 0	Absent =1	Present =2

Plantar reflexes:							
Not tested = 0	Normal ↓ =1	No response =2	Abnormal ↑=3	Not tested = 0	Normal ↓ =1	No response =2	Abnormal ↑=3

Neurological Status	Normal = 0	Unspecified signs = 1	Abnormal (signs of CP) = 2

Cerebral palsy	No =0	High risk =1	Definitely =2	Unclear

Comments:

GMFCS level (0-2 years scale)	I =1 / II =2 / III =3 / IV= 4 / V= 5	
MACs level (1-4 year scale)	I =1 / II =2 / III =3 / IV= 4 / V= 5	
Upper limb/ Handedness	Right predominant =0 Left predominant =1 Bilateral =2	

FAS SYMPTOMOLOGY

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Sentinel Facial Features

Assess for the 3 sentinel facial features of Fetal Alcohol Spectrum Disorder: short palpebral fissure length (2 SD or more below the mean), smooth philtrum (rank 4 or 5 on the Lip-Philtrum guide), and thin upper lip (rank 4 or 5 on the Lip-Philtrum guide).

Palpebral Fissure Length (PFL)

	Right PFL		Left PFL		Mean PFL	
Assessment method	mm	Z score (SD)	mm	Z score	mm	Z score*
☐direct measure ☐ photo analysis						
☐direct measure ☐ photo analysis						
PFL reference chart used: ☐ Stromland ☐ Clarren ☐ Other						

Philtrum

Assessment method	UW Lip-Philtrum Guide 5-point rank
☐direct measure ☐ photo analysis	
☐direct measure ☐ photo analysis	
☐direct measure ☐ photo analysis	

Upper lip

Assessment method	UW Lip-Philtrum Guide 5-point rank
☐direct measure ☐ photo analysis	
☐direct measure ☐ photo analysis	
☐direct measure ☐ photo analysis	

Lip-Philtrum Guide† used: ☐ Guide 1. Caucasian ☐ Guide 2. African American

Sentinel Facial Features Summary

Number of Sentinel Facial Features (PFL 2 SD or more below the mean, philtrum rank 4 or 5, upper lip rank 4 or 5):

☐ 0 ☐ 1 ☐ 2 ☐ 3

Functional Neurodevelopmental Domain Summaries

Assess evidence of significant CNS dysfunction due to underlying brain damage. Required evidence includes severe neurodevelopmental impairment (2 SD or more below the mean or < the 3rd percentile) in domains of brain function based on standardised psychometric assessment by a qualified professional.

1. Neurological

Test/subtest name	Age/ Date	Score	%ile/SD	Interpretation
Other information:				
Motor Skills impairment: ☐ None ☐ Some ☐ Severe ☐ Not assessed				

2. Motor skills

Test/subtest name	Age/ Date	Score	%ile/SD	Interpretation
Other information:				
Motor Skills impairment: ☐ None ☐ Some ☐ Severe ☐ Not assessed				

3. Cognition

Test/subtest name	Age/ Date	Score	%ile/SD	Interpretation
Other information:				
Cognition impairment: ☐ None ☐ Some ☐ Severe ☐ Not assessed				

4. Language

(Expressive and Receptive)

Test/subtest name	Age/Date	Score	%ile/SD	Interpretation
Other information:				
Language impairment ☐ None ☐ Some ☐ Severe ☐ Not assessed				

5. Adaptive Behaviour, Social skills or Social Communication

Test/subtest name	Age/ Date	Score	%ile/SD	Interpretation
Other information:				
Adaptive behaviour, social skills, or social communication impairment ☐ None ☐ Some ☐ Severe ☐ Not assessed				

Neurodevelopmental Summary

Number of neurodevelopmental domains with evidence of severe impairment:

☐ None ☐ 1 ☐ 2 ☐ 3 or more(specify)

FAS	No =0	High risk of FAS =1	Definitely =2	Unclear

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ASD SYMPTOMOLOGY

Item	Score				
Visual Tracking	☐ 0	☐ 1	☐ 2		☐ 8
Disengagement of attentions	☐ 0	☐ 1	☐ 2		☐ 8
Orientation to name	☐ 0	☐ 1	☐ 2		☐ 8
Differential response to facial emotion	☐ 0	☐ 1	☐ 2		☐ 8
Anticipatory social response	☐ 0	☐ 1	☐ 2	☐ 3	☐ 8
Imitation	☐ 0	☐ 1	☐ 2		☐ 8
Social Babbing	☐ 0	☐ 1	☐ 2	☐ 3	☐ 8
Eye Contact	☐ 0		☐ 2		☐ 8
Reciprocal social smile	☐ 0	☐ 1	☐ 2	☐ 3	☐ 8
Coordination of eye gaze	☐ 0	☐ 1	☐ 2	☐ 3	☐ 8
Behavioural Reactivity	☐ 0	☐ 1	☐ 2	☐ 3	☐ 8
Social interest and shared affect	☐ 0	☐ 1	☐ 2	☐ 3	☐ 8
Transitions	☐ 0	☐ 1	☐ 2		☐ 8
Motor control	☐ 0	☐ 1	☐ 2		☐ 8
Atypical motor behaviour	☐ 0		☐ 2		☐ 8
Engagement of attention	☐ 0	☐ 1	☐ 2		☐ 8
Insistence on specific objects/activities	☐ 0	☐ 1	☐ 2		☐ 8
Sharing Interest	☐ 0	☐ 1	☐ 2		☐ 8
Total score					

ASD	No =0	High risk of ASD =1	Definitely =2	Unclear

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12-Month Medical Assessment- Blinded Differential Diagnosis

Study ID: ☐☐☐ **Date:** ☐☐/☐☐/☐☐☐☐

Completed by:

Cerebral palsy	No =0	High risk =1	Definitely =2	Unclear
Motor type	**Primary**		**Secondary**	
	Spastic =1		Spastic =1	
	dyskinetic- dystonic =2		dyskinetic- dystonic =2	
	dyskinetic- choreoathetotic =3		dyskinetic- choreoathetotic =3	
	Hypotonic =4		Hypotonic =4	
	Ataxic =5		Ataxic =5	
Distribution	Bilateral =1 / unilateral =2		Bilateral =1 / unilateral =2	
	No of limbs 1 / 2 / 3 / 4		No of limbs 1 / 2 / 3 / 4	
GMFCS level (0-2 years scale)	I =1 / II =2 / III =3 / IV= 4 / V= 5			
MACs level (1-4 year scale)	I =1 / II =2 / III =3 / IV= 4 / V= 5			
Comments				

FAS	No =0	High risk of FAS =1	Definitely =2	Unclear
Comments				

ASD	No =0	High risk of ASD =1	Definitely =2	Unclear
Comments				

S3: LEAP – CP Medical and Allied Health Resource Form

Study ID: ☐☐☐ **Date:** ☐☐/☐☐/☐☐☐☐
Form completed by: **Interviewer initials:** ☐☐

Allied Health

During the last 6 months have you received treatment or advice from:

1. Physiotherapy	O Yes O No
Does it emphasise	O Motor learning O Equipment O Functional therapy O Stretching & positioning O Other: _____
How often	☐☐ Visits per 6 months
Format	O Individual O Group O Home program
Location	O Hospital O Community O Home O Private practice

2. Occupational therapy	O Yes O No
Does it emphasise	O Motor learning O Equipment O Functional therapy O Stretching & positioning O Other: _____
How often	☐☐ Visits per 6 months
Format	O Individual O Group O Home program
Location	O Hospital O Community O Home O Private practice

3. Speech therapy	O Yes O No
Does it emphasise	O Speech/ talking O Early communication skills (play) O Sign/ symbol O Mealtime O Other: _____
How often	☐☐ Visits per 6 months
Format	O Individual O Group O Home program
Location	O Hospital O Community O Home O Private practice

4. Other	O Yes O No
What does it emphasise?	
How often	☐☐ Visits per 6 months
Format	O Individual O Group O Home program
Location	O Hospital O Community O Home O Private practice

Medical

During the last fortnight, has your child been sick? O Yes ☐☐ (number of days) O No

During the 6 months, has your child had:

1. Admission to hospital	O Yes O No Number of admissions ☐
Visit 1	Reason: Treatment/ investigation: Length of stay ☐☐ days
Visit 2	Reason: Treatment/ investigation: Length of stay ☐☐ days
Visit 3	Reason: Treatment/ investigation: Length of stay ☐☐ days
Visit 4	Reason: Treatment/ investigation: Length of stay ☐☐ days

2. GP appointment	O Yes O No Number of appointments ☐
Visit 1	Reason: Treatment/ investigation:
Visit 2	Reason: Treatment/ investigation:
Visit 3	Reason: Treatment/ investigation:

Visit 4	Reason: Treatment/ investigation:

3. Paediatrician	O Yes O No Number of appointments ☐
Visit 1	Reason: Treatment/ investigation:
Visit 2	Reason: Treatment/ investigation:
Visit 3	Reason: Treatment/ investigation:
Visit 4	Reason: Treatment/ investigation:

4. Other specialist Who:	O Yes O No Number of appointments ☐
Visit 1	Reason: Treatment/ investigation:
Visit 2	Reason: Treatment/ investigation:
Visit 3	Reason: Treatment/ investigation:
Visit 4	Reason: Treatment/ investigation:

5. Other specialist Who:	O Yes O No Number of appointments ☐
Visit 1	Reason: Treatment/ investigation:
Visit 2	Reason: Treatment/ investigation:
Visit 3	Reason: Treatment/ investigation:
Visit 4	Reason: Treatment/ investigation:

6. Other specialist Who:	O Yes O No Number of appointments ☐
Visit 1	Reason: Treatment/ investigation:
Visit 2	Reason: Treatment/ investigation:
Visit 3	Reason: Treatment/ investigation:
Visit 4	Reason: Treatment/ investigation:

Equipment

Has your child been provided with any equipment:

- ☐ Supportive chair/ seating
- ☐ Walking aids
- ☐ standing frame
- ☐ Splints / orthoses
- ☐ Wheelchair

National Disability Insurance Scheme (NDIS) Funding

Does your child have an NDIS plan?	O Yes O No
Is the plan self managed?	O Yes O No
What are you able to use your funding for?	O Therapy (eg physiotherapy, OT) O Equipment (eg walking aid/ orthoses) O Consumables (eg feeding tubes)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1 and 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3-7
Objectives	3	State specific objectives, including any prespecified hypotheses	7-9
Methods			
Study design	4	Present key elements of study design early in the paper	9
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	9-13
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	10-13
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	10, 13-20,
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	13-20
Bias	9	Describe any efforts to address potential sources of bias	21
Study size	10	Explain how the study size was arrived at	10-11
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	N/A
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	20
		(*b*) Describe any methods used to examine subgroups and interactions	N/A
		(*c*) Explain how missing data were addressed	N/A
		(*d*) If applicable, explain how loss to follow-up was addressed	N/A
		(*e*) Describe any sensitivity analyses	N/A
Results			N/A

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	N/A
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	N/A
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) Summarise follow-up time (eg, average and total amount)	N/A
Outcome data	15*	Report numbers of outcome events or summary measures over time	N/A
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	N/A
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	N/A
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	N/A
Generalisability	21	Discuss the generalisability (external validity) of the study results	N/A
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	24

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.