PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	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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VERSION 1 – REVIEW

REVIEWER	Scattoni, Maria Luisa Istituto Superiore di Sanità, Research Coordination and Support Service
REVIEW RETURNED	17-Jun-2021

GENERAL COMMENTS	In the included criteria and in the data collection survey, authors may consider including if children enrolled in the study are siblings of children already diagnosed with NDD since it is a high-risk population for NDD. I suggest defining CP, ASD, and FASD in the abstract It could be beneficial that at 12 months CA infants will be assessed by a child neuropsychiatrist, with the pediatrician (if this is possible in Australia). The neuropsychiatrist and the pediatrician can benefit from the use of DSM-V for documenting the presence of any symptomatology. Regard the GM assessment, the use of detailed tools both in the writhing period and in the fidgety period is unclear. As the MOS will be assessed in the fidgety period, please specify if "General Movements Optimality Score " (Christa Einspieler, Peter B Marschik and Yayohi Nakajima 2004/2008) will be assessed in the writhing period and if not please specify the reasons.

VERSION 1 – AUTHOR RESPONSE

1. Patient and Public Involvement: We have implemented an additional requirement to all articles to include the 'Patient and Public Involvement statement within the main text of your main document. Please refer below for more information regarding this new instruction

Response: We have added a Patient and Public involvement statement to the methods section (pg.11-12) as:
"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.
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."

- We have included an acknowledgement of contributions (pg.24) as

"We acknowledge the key contributions of the Aboriginal and Torres Strait Islander peoples who have engaged, provided consultation and co-design to the cultural framework and study design and have shared knowledge to ensure the cultural sensitivity and safety of the program, to reflect key concepts of being, knowing and doing. In particular key community stakeholders from Gurriny Yealamucka health service, Apunipima Cape York Health council and community members with lived experience who have shared their stories and expertise."

2. In the included criteria and data collection survey, authors may consider including if children enrolled in the study are siblings of children already diagnosed with NDD since it is a high-risk population for NDD.

Response: The family history of adverse neurodevelopmental outcomes (NDOs) are part of the study inclusion criteria (pg. 10) We have added "and/or sibling with a diagnosed NDD" to ensure this is a clear inclusion criteria.
This now reads as:
"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."

- Information regarding family history of NDD and/or adverse NDO is collected as part of the medical, perinatal and demographic data (S1_LEAP-CP medical checklist: Part 1 and 2, pg.7).

3. I suggest defining CP, ASD, and FASD in the abstract
Response: Neurodevelopmental disorders are now defined in the introduction section of the abstract, which now reads as:

“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.”

We have not specifically defined CP, ASD, FASD, due to the wordcount advised for the abstract. These are defined in detail in the main text, introduction section on pages 4-6. Cerebral Palsy (pg. 4, paragraph 1), Autism Spectrum disorder (pg. 5, paragraph 1) and Fetal Alcohol Spectrum Disorder (pg. 6, paragraph 1.)

4. It could be beneficial that at 12 months CA infants will be assessed by a child neuropsychiatrist, with paediatrician (if this is possible in Australia). The neuropsychiatrist and the paediatrician can benefit from the use of DSM-V for documenting the presence of any symptomology
Response: At 12 months corrected age infants in the study will be assessed by their consultant Paediatrician, who would use DSM-V as part of their documentation of ASD Symptomology. Unfortunately, in general neuropsychiatrist’s are not available in these regional centres in Queensland.

5. Regarding the GM assessment, the use of detailed tools both in the writhing and fidgety period is unclear.
As the MOS will be assessed in the fidgety period, please specify if “General Movements Optimality Score” (Christa Einspieler, Peter B Marschik and Yayohi Nakajima 2004/2008) will be assessed in the writhing period and if not please specify the reasons.
Response: Infants can be recruited to the study from birth - 9 months corrected age. As not all infants will be recruited within the appropriate timeframe to complete a writhing GMA (birth to 4 weeks post term and because the Writhing Period GMs are less predictive of outcome (Spittle et al. 2009, Spittle et al. 2013, George et al. 2021), we have decided to focus on fidgety age for the General Movements Assessment (GMA). In addition, the Fidgety GMA (3 – 5 months CA) are more predictive of outcomes (Novak et al 2017, Morgan et al 2019, Einspieler et al 2020). Where possible depending on the age of recruitment we will endeavour to collect a writhing GMA video close to term equivalent age for infants who are recruited within the correct timeframe and will be utilised as part of the infant’s GMA trajectory (page 12). The more detailed analysis using the General Movements Optimality Score (GMOS) will not be completed on the writhing videos as this requires more advanced training.

- We have included an amendment on page 14, to improve the clarity of the General movements assessment. This now reads as:
“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.”

- The use of MOS during fidgety period only is detailed on pages 14 and 15.

“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.”

6. Please name the ethics committees that approved the study in the Ethics and Dissemination section of the abstract.
Response: the names of all approved ethics committees to the ethics and dissemination section of the abstract (pg. 2) This now reads as:
“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.”

Please note, due to the advised amendments to the abstract it is now 391 words. The abstract included in the updated clean copy document is the full abstract (main document: LEAP CP_prospective cohort study_protocol_revised clean copy_06.12.2021) The abstract submitted in “step 2: Type, title and abstract” is a modified version (300 words) to allow for the manuscript to be submitted.

7. Please revise the ‘Strengths and limitations’ section of your manuscript (after the abstract). This section should contain up to five short bullet points, no longer than one sentence each, that relate specifically to the methods. The aims or anticipated results of the study should not be summarised here.
Response: This section has been amended to reflect the specified editor’s comments (pg. 2) and now reads as:
“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."

8. Please mark any items on the STROBE checklist that are not relevant to a protocol (e.g. results) as 'n/a'.
Response: The STROBE checklist has been amended as suggested. (See attachment: STROBE_checklist_BMJ-Open_cohort-studies_protocol_CarlyLuke_03.12.21)

9. Please include the planned start and end dates for the study in the methods section.
Response: These dates have been added to the study design section of the methods (pg. 10). This now reads as:
"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]."