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Early Moves: A protocol for a population-based prospective cohort study to identify early biomarker of cognitive impairment in infants.

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Abstract:

Introduction:

The current traditional diagnostic pathways for cognitive impairment rarely identify babies at risk of cognitive impairment before 2 years of age. Without very early detection and timely targeted intervention, these children and their families have poorer health outcomes and do not reach their full life potential. *Early Moves* aims to identify early biomarkers, including General Movements (GMs), for babies at risk of cognitive impairment, allowing early intervention within critical developmental windows to enable these children to have the best possible start to life.

Method and analysis:

Early Moves is a double masked prospective cohort study that will recruit 3,000 babies. *Early Moves* will determine the diagnostic value of abnormal GMs (at writhing and fidgety age) for mild, moderate and severe cognitive delay at two-years measured by the Bayley-4. Parents will use a novel smart-phone app called Baby Moves to video their babies' GMs. Trained GMs assessors will be masked to any risk factors and assessors of the outcome will be masked to the GMs result. Automated scoring of GMs will be developed through applying machine-based learning to the data and the predictive value for an abnormal GM will be investigated. Screening algorithms for identification of children at risk of cognitive impairment, using the GM Assessment (GMA), and routinely collected social and environmental profile data will be developed to allow more accurate prediction of cognitive outcome at 2 years. A cost evaluation for GMA implementation in preparation for national implementation will be undertaken including exploring the relationship between cognitive status and health care utilisation, medical costs, health-related quality of life and caregiver burden.

Ethics and dissemination:

Ethics approval has been granted by the Medical Research Ethics Committee of Joondalup Health Services and the Health Service Human Research Ethics Committee (1902) of Curtin University (HRE2019-0739).

Trial registration number: ACTRN12619001422112

Article Summary

Strengths and limitations of this study:

- This is the first population based prospective cohort study investigating the utility of the General Movements assessment as a biomarker to identify children with cognitive impairment during early infancy.
- This is the first study to explore the feasibility of using smart phone app based video collection of GMs in a large population.
- This study will develop automated scoring of the GMs using machine learning making wide scale screening possible in the future.
- This study will combine the GMA outcome, with routinely collected demographic and health data to develop a screening algorithm for identification of infants at risk of cognitive impairment.
- This study is limited by its exclusion of families with limited English language.

Key Words (MeSH Terms):

- Cognitive Dysfunction
- Infant
- Child Development
- Cohort Studies
- Neonatal Screening

Introduction

Neurodevelopmental disorders (NDD) result from changes in the brain that lead to a delay in skill development, including cognitive, language and motor impairments. The lifelong impact of NDD has enormous personal and financial burden on the individual, their family and the community. In Australia, the cost of intellectual disability (also referred to as cognitive impairment) alone, is estimated to be $14,720 billion annually [1].

The first two years of life are a critical period for motor and cognitive development due to the timing of corticospinal tract development and the plasticity mechanisms at work in the infant's brain [2]. Thus, the earlier cognitive impairment can be detected, the greater the potential benefits of ensuing early interventions for optimising neuroplasticity, preventing or ameliorating neurodevelopmental disorders and enhancing parental wellbeing. At present it is difficult to accurately diagnose infants at risk of cognitive impairment [3-6]. Considerable delay between parents' first concerns and confirmation of a diagnosis is often reported [7]. This is more pronounced for those residing outside major centres, with a known health inequality in regional and rural Australia, and in poorly served outer metropolitan areas of large cities [8].

General Movements (GMs) are a distinct spontaneous movement pattern evident in babies before and after birth[9], with writhing GMs observed in utero up to 8 weeks post-partum, and fidgety GMs which are present from 8 to 20 weeks' post-term [10]. General Movements are now recognised as a sensitive tool for providing information on the health of a baby's brain function [11, 12]. The absence of fidgety GMs is the best predictor of cerebral palsy in high-risk infants, with pooled estimates of 98% sensitivity and 91% specificity [12].

While the GMs are accurate for predicting motor impairment, recent evidence suggests GMs may be a biomarker for identifying cognitive impairment in preterm infants [13, 14]. In two systematic reviews higher risk of cognitive impairment was associated with persistence of abnormal writhing GMs until 8 weeks after term and with monotonous movement sequences and postural abnormalities at 3-5 months. Further, the developmental quotient at 2-3 years of children born preterm, with abnormal writhing GMs at 1 month post-term, was lower than gestation and age matched infants with normal writhing GMs [14].

Abnormal fidgety GMs in preterm infants was also found to be associated with a score on average eight points lower on the Bayley Scales of Infant and Toddler Development–Second Edition at two years of age compared to those with normal fidgety GMs [15]. This difference in cognition was greater when the children were reassessed at age four years on the Differential Ability Scale [15]. These findings indicate that abnormal spontaneous movement patterns, at both the writhing and fidgety stages, may presage later cognitive impairment. The majority of this evidence however exists in preterm and high-risk infants; there is a paucity of information for healthy term infants.

More detailed scoring of the GM, in which every movement criterion is given a score [16] is known as the GM Optimality Score (GMOS) at the writhing age [17], and the Motor Optimality Score (MOS) at the fidgety age [18]. A higher score represents more optimal movements. In a study of 40 extremely preterm infants, only six out of 33 infants that showed normal fidgety movements, were found to have the highest MOS score possible [19], highlighting the increased sensitivity of optimality scoring compared to global GMA.

Should GMs be shown to be an early biomarker for cognitive impairment, there are still barriers to implementing GMA as a population level screening tool. These barriers include access to trained assessors in many locations, and the cost involved in videoing of the infant. To overcome these barriers, a smart-phone app called Baby Moves has been developed allowing families or health professionals to record and upload GM recordings directly [20], removing the need for in-person appointments.

The use of machine based movement recognition, aimed at automatic detection, classification and quality assessments of limb movements has the potential to further reduce the time and financial costs of GM assessments. This approach has been explored by a number of researchers aiming to automate reporting of fidgety GMs [21-26]. Results suggest automated readings of fidgety movements are feasible, reporting sensitivity and specificity of 79-85% and 63-71% respectively [21-23]. Automated video analysis may provide a low-cost, high sensitivity approach by combining the sensitivity of advanced machine classification as a primary screening mechanism, and the specificity of human expert opinion on videos classified as high risk by the automation.

It is known that a child's biological and environmental profile is related to developmental outcomes [27-29]. A number of protective and risk factors, particularly birth weight, gender and prematurity, and maternal age are routinely collected and documented. Applying a bioecological model [30] to explore developmental vulnerability using routinely collected data, in conjunction with GM assessments may provide a stronger predictive tool than GM's alone creating a robust and meaningful screening tool [27].

Identification of an early biomarker, along with the development and validation of an accessible affordable and scalable screening tool, for the early identification of cognitive impairment would allow a greater number of infants to receive effective early interventions during the critical window of brain development: an advantage to the child, family and greater society.

"The economic benefit [of early detection and intervention] could be great, but the benefit to the families is priceless"

-Kids Rehab WA Consumer group member

Aims and Hypothesis

Phase One – GMA as a biomarker

The primary aim of phase one is to determine the diagnostic value of abnormal GMs for cognitive delay at two-years.

It is hypothesised that abnormal GMs will be predictive of cognitive delay at two years. As this is the first study to look at the predictive ability of GMA for cognitive delay or impairment in a large birth cohort of majority low risk infants, we have insufficient data to hypothesise the diagnostic test accuracy.

The secondary aim of phase one is to develop automated scoring of the GMA through applying machine based learning to the data. It is hypothesised that automated scoring of GMA will have >90% specificity and >85% specificity to detect GM abnormalities, with lower accuracy for optimality scores.

Phase Two – Screening algorithm

The primary aim of phase two is to develop screening algorithms for identification of children at risk of cognitive impairment, using the GMA, and routinely collected social and environmental profile data.

It is hypothesised an algorithm of early child, family and societal risk factors and GMA and optimality scores, will be a more accurate predictor of cognitive status at 2 years corrected age than GMA or optimality scores alone.

Phase Three – Cost and economic evaluations

The primary aim of phase three is to conduct a cost evaluation for GMA implementation from the perspective of the funder in preparation for national implementation.

The secondary aim of phase three is to assess the relationship between cognitive status and health care utilisation, medical costs, health-related quality of life and caregiver burden.

It is hypothesised cognitive impairment will predict; higher health care utilisation and direct medical costs, poorer health-related quality of life and higher caregiver burden.

Methods

Study Design

This study is a double-masked, prospective cohort study of 3,000 babies. The methodological design of this cohort study has been informed by the 2007 "Strengthening the Reporting of Observational Studies in Epidemiology" (STROBE) checklist for cohort studies [31]. The methodological design of phase one (a study of diagnostic test accuracy), was informed by the 2015 "Standard for Reporting of Diagnostic Accuracy Studies" (STARD) checklist [32].

Setting

This study is a sub-study of the ORIGINS project, a major Western Australian cohort study of 10,000 families, with detailed data and sample collection, including environmental and biological profiling on 5,000 families. It is the largest representative sample of Australian infants (preterm and term born) [33]. Participants are recruited in to one of two arms of the ORIGINS study:

1. Non-active participants: Consent to use of de-identified databank and biobank information available via routine hospital data collections and data linkage to both WA and Australian Government Data.
2. Active Participants: In addition to the above, additional lifestyle and environmental data via online questionaries, biological sampling and infant follow-up at specific time points which is not part of standard care, are collected.

Recruitment

Early Moves will recruit a total of 3,000 infants who are enrolled in The ORIGINS Project between November 2019 and December 2022, with a least 2,000 infants from the Active Participant arm of ORIGINS. Recruitment can occur at any time, up until discharge from hospital after the birth of the baby. To reduce risk of self-selection bias on the basis of birth experience, antenatal recruitment will targeted where possible (Figure 1). Timing of consent relative to birth will be recorded.

Inclusion Criteria

a) Mother intending on birthing/have recently birthed at Joondalup Health Campus between 2019 and 2022
b) Enrolled in the ORIGINS project

Exclusion Criteria

a) Babies enrolled in an ORIGINS intervention study that has a primary cognitive or language outcome

Masking

The assessors will be masked to baby's gestation at birth; birth, medical and social history and the results of any of the ORIGINS or *Early Moves* outcomes. Abnormalities in serial GM assessments are known to be predictive of cerebral palsy, so in cases where abnormalities are identified, the participants will be notified and referred to the appropriate clinical services for further investigation and management. Based on rate of cerebral palsy in Australia of 1.4 per 1000 live births [34], we anticipate to identify approximately 5 cases of cerebral palsy, where parents will be unmasked to GM outcomes as per above protocol.

Bias

As a prospective cohort study selection bias is minimised as participants will enrol prior to or very soon after the birth of the baby. The ORIGINS project [33] has a number of effective strategies in place to reduce loss to follow up. The Ages and Stages Questionnaire, a developmental screening tool administered as part of ORIGINS [33], will be used to explore study bias for any children lost to follow up in the *Early Moves* study within the active cohort.

Phase One: Predictive Variables

General Movements will be obtained using the Baby Moves smartphone app. A 3 minute video is taken using the app with the baby lying on a plain, flat surface in an awake, settled state. Videos are securely uploaded to the study database for remote assessment by the GM assessors according to Prechtl's GMA, and calculation of GMOS [16, 17] and MOS [16, 18]. The Baby Moves app has been successfully piloted at the fidgety period on 446 infants to determine feasibility [20, 35], with 69.9% - 82.7% of the videos taken by families scorable [35]. This study seeks to reduce the proportion of un-scorable videos to 15% by employing personalised training and parental education, instructional films and the use of e-reminders of upcoming and currently due videos, and phone support. Further, as this study commences with the first video made within 2 weeks post-term rather than 12 weeks post-term, we anticipate families will be more engaged with the study compared with early studies using the Baby Moves app. Videos received will be reviewed within two weeks of submission to check for quality, and families will be contacted via phone if the video is un-scorable. Collection of two videos within each time period further increases the likelihood of one scorable video being attained within each time period.

Remote GMA will be conducted for each of the two time periods, (Figure 1). For the purpose of exploring the predictive ability of GM on cognitive impairment, assessment will be conducted on the first video, with the second video used if a) the first is not scorable, or b) there is uncertainty around classification and further video footage is required to make a final decision.

1. Time-period 1 "Writhing" – videos collected at 1 to 2+6 and 3 to 4+6 weeks post-term age. Movements will be classified, and GMOS calculated.
2. Time-period 2 "Fidgety" – videos collected at 12 to 13+6 and 14 to 16 +6 weeks post-term age. Movements will be classified and MOS calculated.

General Movement Fidelity

General Movement Assessments will be conducted by qualified and registered clinicians who have experience in reporting GMA's and have passed the advanced GMs course by the General Movements Trust. The assessors must have experience in clinical and research application of GM assessment prior to involvement in the study.

Each GM and GMOS/MOS assessment will be conducted by two individual assessors. If there is disagreement between the two assessors a third blinded, experienced GM Instructor (ASp or CM), will make the final decision. Disagreement is defined as difference in GM categorical assessment, or optimality scores of more than five point difference [36].

The interrater reliability of the three assessors for GMA will be accepted as "almost perfect" (≥82% of data are reliable, with Cohen's Kappa > 0.9). Interrater reliability and agreement for GMOS and MOS will be accepted as "excellent reliability" (intraclass correlation coefficient of >0.9 using two-way random effects ANOVA) [37]. This will be done by triple scoring the first 10 videos, then 10% (selected at random) of each block of 100 videos until criteria for reliability are met. To ensure reliability is maintained throughout the study, a random selection of 10 videos out of every 300 will be triple scored.

Automated reading of GMA

Advanced machine learning methods have been developed to classify and separate normal versus abnormal videotaped fidgety GM [35, 38]. Video recordings are processed using a pipeline of computer vision and machine learning techniques to predict GMA. Salient point detection (where the joints related to the GM of the infant are located and tracked in the video frames) is followed by extraction of the local motions of the joints into feature vectors. These feature vectors are automatically classified using our anomaly detection algorithm developed during pilot work [38, 39]. Based on a *k* – nearest neighbour classification approach on 265 video recordings of babies, and a feature based on the histogram of the optical flow, the accuracy for automated GMA is 72.9% [39].

Table 1 Source of routinely collected demographic and health factors used for the development of screening algorithms in Phase Two. Factors are grouped according to levels, employing a bioecological model of child development. JHC: Joondalup Health Campus

Phase One: Primary Outcomes

The

	Midwives Notification System	JHC Mother's Health Questionnaire
Cultural and Neighbourhood Factors		
Socioeconomic Index (SEIFA)	√	
Ethnicity	√	
Parent/Family Factors		
Marital status	√	√
Smoking during pregnancy	√	√
Alcohol consumption during pregnancy	√	√
Illicit drug use during pregnancy		√
Maternal Medical Conditions	√	
Maternal Mental Health Conditions		√
Perinatal Mental Health Risk Factors	√	
Child/Biological Factors		
Pregnancy complications	√	√
Family History of Developmental Difficulties		√
Method of Birth	√	
Complications of labour and birth	√	
Gender	√	
Infant Weight	√	
Resuscitation	√	
Estimated Gestation	√	
Birth defects	√	
Birth trauma	√	
Special care number of days	√	
Plurality	√	

Bayley Scales of Infant and Toddler Development- 4 (Bayley-4) [40] is the most frequently used test in infant developmental assessments. Bayley-4 cognitive and language score is the primary outcome at 2 years corrected age. Cognitive delay will be defined as mild (when the Bayley-4 cognitive and language score falls between 1

and 2SD below the Australian mean), moderate (score between 2 and 3SD below the Australian mean) or severe (score more than 3SD below the Australian mean) [41]. Children unable to complete psychological testing because of presumed severe cognitive delay will be assigned a score of -4 SD. If babies score <-2SD on the Bayley-4 across any domain, they will be referred to the appropriate developmental services for further investigation and management.

Phase Two: Screening Algorithms

Screening algorithms for identifying children requiring early intervention for cognitive delay will be developed using data available from the Joondalup Health Campus (JHC) Mothers Health Questionnaire (routinely administered to all mothers intending to birth a JHC), and the Midwives Notification System (Table 1). Linked data from the Western Australian Register of Developmental Anomalies at age 1 year will be utilised.

Phase Three: Health Economics

Health care resources will be measured and standard cost sources will be used to apply unit costs to resources. Costs will be standardised to a reference year and future costs will be discounted according to standard practice. Resources and associated costs will include GMA and Bayley-4. The cost of GMA will include ongoing cost of the app and labour resources required for assessment of the videos. Health-related resource use data collected will include screening assessments, therapy frequency and duration (traditional/alternate), hospital admissions, GP and medical specialist visits, medications and equipment. Data will be collected via the Health Resource use (HRU) questionnaire [42], supplemented by consented access to individual hospital, Medical Benefits Scheme (MBS) and Pharmaceutical Benefits

Scheme (PBS) records.

The *Carer Experience Scale (CES)* will be employed as a measure of caregiver burden. This validated measure of care-related quality of life has six domains (activities, support, assistance, fulfilment, control and relationship with the care recipient) and takes approximately 3 minutes to complete [43]. The Carer Experience Scale is scored from an algorithm derived from preferences of the general population and can be used to value carer outcomes in economic evaluation using index values [43].

Sample Size Estimation

Early Moves is a single masked prospective cohort study and will recruit 3,000 babies sufficient to establish >90% sensitivity and >94% specificity (alpha 0.05 and assuming actual sensitivity and specificity = 92.5% and 95%, 15% attrition, 15% non-readable images). For secondary outcomes, there is sufficiently high power to detect even small associations between early GM results and Bayley-4 interval scores at 2years. For example if 90% of children have normal GMs as infants, the study is powered to detect between group (GM normal vs abnormal) differences on the Bayley- 4 (cognitive and language) at 2 years of 3.5 points or greater with 90% power (assuming alpha=0.05, and SD=15 points).

Statistical Analysis

Summary statistics will be described using either mean (standard deviation) or median (25th-75th percentile) for continuous variables, according to distribution, or as frequency (percentage) for categorical variables.

For Phase One, the primary aim will be assessed using standard diagnostic statistics (e.g. sensitivity, specificity, predictive values, and likelihood ratios). The predictive validity of the GM categorical classification will be established using logistic regression. The diagnostic value of machine learning for identifying GM writhing and fidgety categorical classification will be evaluated by determining the accuracy, precision, recall and area under the curve (AUC) of both automated machine assessment and machine-human hybrid assessment using the entire dataset of videos (n=6000). An algorithm for early diagnosis of cognitive impairment will be developed using logistic regression modelling, using variables from the GMOS/MOS, GMA categorical classification. Variables will be entered using forward selection based on the Wald statistic. Sensitivity and specificity of the regression model, with 95% confidence intervals will be established.

For Phase Two, screening algorithms based on the association between measurements recorded at birth or in infancy (e.g. GM category) and measurements recorded at 2 years will be assessed using linear regression for interval outcome data, logistic regression for binary outcome data, and Poisson regression for count outcome data. Hierarchical mixed-effects models will be used with 'participant' included in the model as a random effect in order to account for the non-independence of observations from the same participant. Motor impairment will be tested as a

potentially confounding variable for all models. Variables will be selected for potential inclusion in multivariable models based on univariable significance at the $p<0.2$ level. Multivariable models will be built in a step-wise manner with redundant variables eliminated using Akaike's and Schwarz's Bayesian criteria. Interactions will be investigated as appropriate.

For Phase Three, cost and economic evaluations will consider service use and service costs. We will describe patterns of met and unmet need in the study children, and indirect costs to families will be examined. Associations between costs and all other outcome variables, including those related to cognitive outcome will be assessed, with adjustment for confounders.

Ethics and dissemination

The ORIGINS Project (ref. #1440) and *Early Moves* (ref. #1902) has been approved by the Human Research Ethics Committee of JHC. Participant information booklets will be provided to all participants prior to entry into the study, and full written and informed consent will be obtained from all participants.

A collaborative (push, pull, exchange) knowledge translation model has been adopted in this study [44, 45]. Project investigators will champion knowledge translation across five levels of Health: Consumer and Service Providers; Department; Program; and Health Service Level. Specific knowledge translation strategies and skill building activities will be targeted across the phases of the *Early Moves* Project, and in consultation with our stakeholders. This will include, but are not limited to, dissemination of findings to consumers and stakeholders via peer reviewed publication of study results, plain language summaries, newsletter feedback and media case studies, as well as presentations at key national and international conferences.

Public/patient involvement

Community engagement is at the core of the ORIGINS and *Early Moves* projects [33], with the implementation of a collaborative model of involvement [46]. Community members of a clinical consumer reference group were involved in the priority setting for the study, specifically parents of children with cognitive impairment. When asked whether they felt the study was important and worthwhile, the response was very positive, e.g. "Yes, yes, yes. I don't understand why you wouldn't do it." The group

also endorsed time points, methods for collection of data and follow up protocols for abnormal GMA results. Furthermore, ORIGINS has a dedicated community stakeholder coordinator and 12 parents whom form a consumer reference group. This ORIGINS consumer reference group has been involved in development of recruitment and information and consent materials for *Early Moves*. Consumer and community representation is also incorporated in the ORIGINS and *Early Moves* governance structure.

Bidirectional, effective and continuous communication with consumers will guide research directions, interpretation of findings and their implications for policy.

Discussion

At present, early intervention for cognitive impairment is hindered by the lack of early biomarkers to allow accurate early diagnoses or risk identification to occur. *Early Moves* aims to identify early biomarkers for babies at risk of cognitive impairment, allowing early intervention within critical developmental windows to enable babies to have the best possible start to life.

The study has a number of strengths. It is a well powered study with a population-based sample. The recruitment during the antenatal period ensures self-selection bias is minimised where it relates to the birth experience (e.g. prematurity; late pregnancy or birth complications). The assessment variables utilised in this study have proven reliability and validity. As a sub-project of the ORIGINS project, *Early Moves* will have access to biobank data, to generate a detailed biological and environmental risk profile, to inform predictive algorithms, and investigate links between cognitive impairment and biological and environmental factors. The study has strong consumer involvement and an embedded knowledge translation plan which will help guide and facilitate the translation of research findings in to clinical practice.

A potential limitation is that the final outcome measure is conducted at two years. Research in premature babies shows the association between abnormal GMs and cognitive impairment is weaker at 2 years compared to 4 years [15]. The cohort will however be followed until age 5 years as part of the ORIGINS project, with later assessments to include developmental assessments such as Ages and Stages questionnaires and linkage to the Australian Early Development Census (AEDC) providing data on early childhood development at entry to the first year of full time

school. The AEDC is an Australian wide data collection conducted by teachers using the Australian version of the Early Development Instrument. Exclusion of families who do not have sufficient English to complete standardised questionnaires is also a limitation. This exclusion criterion has been set by the ORIGINS study, which does not allow the recruitment of mothers with insufficient English to provide consent if reliance on an interpreter is required. This study is also potentially limited by the single site recruitment. Demographic data will be available to aid in the interpretation of generalisability to other populations.

Early Moves will provide novel care models in rural and remote communities through the use of smart phone technology and machine based learning, facilitating the feasibility of app-based GM assessments as a population wide assessment tool. Through combining automated app-based GM assessments with routinely collected risk and protective factors, employing a bioecological model of development, *Early Moves* recognizes the complex interplays of risk and protective factors to create a robust screening tool for cognitive impairment in infants. Inclusion of health economics evaluation will further enhance the potential for this technology to be translated in to clinical care.

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Conflict of Interest

None declared.

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Author Contributions

CE and JV are the chief investigators and together with CA, ASa, ASp, RNB, NB, CM, DS, EG, and RSW designed established and achieved funding for the research study. AA, AM, DB, MS, RW, SB, SP, SW, VL, SD, AT, LJ, NA, and the Early Moves Clinical Working Party (EMCWP) also contributed to study design. CE, JV and CA are responsible for ethics applications and reporting. CA, DS, and SP are responsible for recruitment. CE, JV, CA, ASa supervise the data collection and implementation of training. CE, JV, ASa, AS, CM, MS, NA and EMCWP are responsible for design and implementation of GM outcomes. NB, CM and VL are responsible for design and implementation of machine learning outcomes. AT, AM, RW, SD and AA are responsible for design and implementation of consumer engagement outcomes. EG is responsible for design and implementation of health economics outcomes. SW, DS and CA are responsible for design and implementation of routinely collected screening outcomes. JV, ASa, and SB are responsible for design and implementation of developmental outcomes. CE, JV, CA, ASa, ASp, RNB, NB, CM, DS, EG, and RSW will take lead roles in preparation for publications on the clinical outcomes of the study. RSW will take on a lead role of statistical analysis for the study. All authors contributed to the preparation of this manuscript and have approved the final version.

Data statement

De-identified individual participant data that underlie the results published in articles resulting from this study will be made available to researchers on a case by case basis, beginning 6 months and ending 5 years following the relevant article publication. Data will be made available to researchers who provide a methodologically sound proposal with appropriate research governance and ethics approvals, for the purposes of achieving aims of approved proposal of for use in meta-analysis. Proposals should be directed to Catherine Elliott Catherine.elliott@curtin.edu.au

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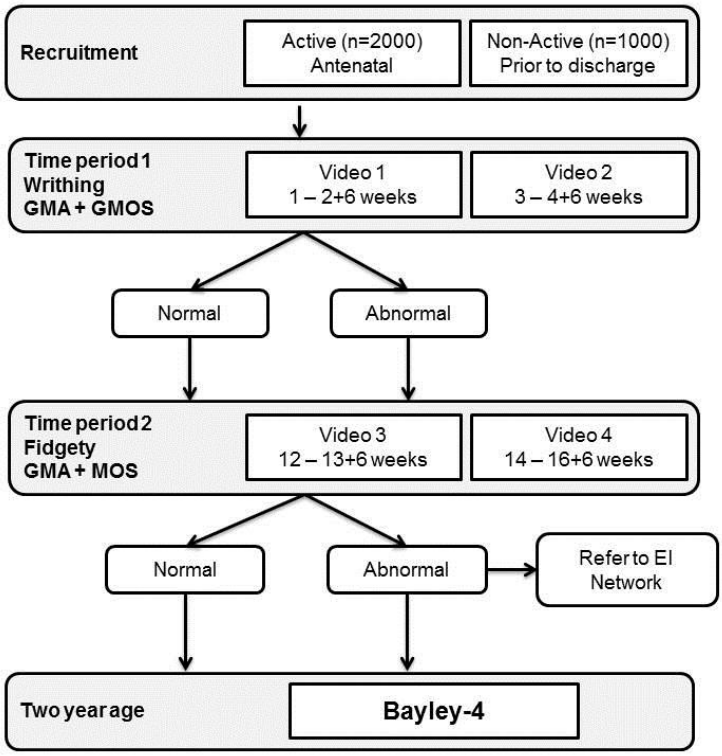

Study assessment timeline. GMA: General Movement Assessment. GMOS: General Movement Optimality Score. MOS: Motor Optimality Score. EI: Early Intervention

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Early Moves: A protocol for a population-based prospective cohort study to establish General Movements as an early biomarker of cognitive impairment in infants.

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Early Moves: A protocol for a population-based prospective cohort study to establish General Movements as an early biomarker of cognitive impairment in infants.

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Abstract:

Introduction:

The current diagnostic pathways for cognitive impairment rarely identify babies at risk before 2 years of age. Very early detection and timely targeted intervention, has potential to improve outcomes for these children and support them to reach their full life potential. *Early Moves* aims to identify early biomarkers, including General Movements (GMs), for babies at risk of cognitive impairment, allowing early intervention within critical developmental windows to enable these children to have the best possible start to life.

Method and analysis:

Early Moves is a double masked prospective cohort study that will recruit 3,000 term and preterm babies from a secondary care setting. *Early Moves* will determine the diagnostic value of abnormal GMs (at writhing and fidgety age) for mild, moderate and severe cognitive delay at two-years measured by the Bayley-4. Parents will use the Baby Moves smart-phone app to video their babies' GMs. Trained GMs assessors will be masked to any risk factors and assessors of the primary outcome will be masked to the GMs result. Automated scoring of GMs will be developed through applying machine-based learning to the data and the predictive value for an abnormal GM will be investigated. Screening algorithms for identification of children at risk of cognitive impairment, using the GM Assessment (GMA), and routinely collected social and environmental profile data will be developed to allow more accurate prediction of cognitive outcome at 2 years. A cost evaluation for GMA implementation in preparation for national implementation will be undertaken including exploring the relationship between cognitive status and health care utilisation, medical costs, health-related quality of life and caregiver burden.

Ethics and dissemination:

Ethics approval has been granted by the Medical Research Ethics Committee of Joondalup Health Services and the Health Service Human Research Ethics Committee (1902) of Curtin University (HRE2019-0739).

Trial registration number: ACTRN12619001422112

Article Summary

Strengths and limitations of this study:

- This is the first population based prospective cohort study investigating the utility of the General Movements assessment as a biomarker to identify children with cognitive impairment during early infancy.
- This is the first study to explore the feasibility of using smart phone app based video collection of writhing and fidgety GMs in a large representative population.
- This study will develop automated scoring of the GMs using machine learning making wide scale screening possible in the future.
- This study will combine the GMA outcome, with routinely collected demographic and health data to develop a screening algorithm for identification of infants at risk of cognitive impairment.

Key Words (MeSH Terms):

- Cognitive Dysfunction
- Infant
- Child Development
- Cohort Studies
- Neonatal Screening

Introduction

Neurodevelopmental disorders (NDD) result from changes in the brain that lead to an impairment in skill development, including cognitive, language and motor skills [1]. The lifelong impact of NDD has enormous personal and financial burden on the individual, their family and the community. Nationally in Australia, the cost of intellectual disability alone, is estimated to be $14,720 billion annually [2]. In Western Australian (WA), 6.6% of children meet the criteria for 'developmentally vulnerable' at school entry with regard to language and cognition [3], while the prevalence of diagnosed intellectual disability in WA children is 14.3/1000 [4].

The first two years of life are a critical period for motor and cognitive development due to the timing of corticospinal tract development and the plasticity mechanisms at work in the infant's brain [5]. Thus, the earlier cognitive impairment can be detected, the greater the potential benefits of ensuing early interventions for optimising neuroplasticity, preventing or ameliorating neurodevelopmental disorders and enhancing parental wellbeing. Early interventions for cognitive development have been explored in preterm and low birth weight infants. Though systematic review of the topic suggests benefits may be restricted to short-term gains [6, 7], comprehensive long term follow up analysis indicates some biological risk factors significantly affect response to the intervention [8]. For example, higher-low birth weight infants stood to gain the more from early intervention with cognitive improvements seen up at 18 years of age compared to lower-low birth weight infants [8, 9].

It remains difficult to accurately identify infants at risk of cognitive impairment [10-13] in the absence of other risk factors such as prematurity or low birth weight, making it impossible to assess interventions for children in the general population at risk of cognitive delay. This lack of identification pathways is highlighted by the considerable delay that is often reported between parents' first concerns and confirmation of a diagnosis [14]. This is more pronounced for those residing outside major centres, with a known health inequality in regional and rural Australia, and in poorly served outer metropolitan areas of large cities [15].

General Movements (GMs) are a distinct spontaneous movement pattern evident in babies before and after birth [16]. Writhing GMs are movement sequences of

variable speed, amplitude and intensity which are observed in utero up to 8 weeks post-partum, with the most significant abnormality involving sudden and synchronised cramping of the trunk and limbs [17]. Fidgety GMs are small twitches at the joints such as fingers, ankle and neck, which are present from 8 to 20 weeks' post-term. The absence of these small twitches is the most notable abnormality seen at this age [18, 19]. General Movements are now recognised as a sensitive tool for providing information on the integrity of a baby's brain function [20, 21]. The absence of fidgety GMs is the best predictor of cerebral palsy in high-risk infants, with pooled estimates of 98% sensitivity and 91% specificity [21].

While the GMs are accurate for predicting motor impairment, recent evidence suggests GMs may be a biomarker for identifying cognitive impairment in preterm infants [22, 23]. In two systematic reviews higher risk of cognitive impairment was associated with persistence of abnormal writhing GMs until 8 weeks after term and with monotonous movement sequences and postural abnormalities at 12-20 weeks. Further, the developmental quotient at 2-3 years of children born preterm, with abnormal writhing GMs at 4 weeks post-term, was lower than gestation and age matched infants with normal writhing GMs [23].

Abnormal fidgety GMs in preterm infants was also found to be associated with a score on average eight points lower on the Bayley Scales of Infant and Toddler Development–Second Edition at two years of age compared to those with normal fidgety GMs [24]. This difference in cognition was greater when the children were reassessed at age four years on the Differential Ability Scale [24]. These findings indicate that abnormal spontaneous movement patterns, at both the writhing and fidgety stages, may presage later cognitive impairment. The majority of this evidence however exists in preterm and high-risk infants; there is a paucity of information for healthy term infants.

More detailed scoring of the GM, in which every movement criterion are given a score [25] is known as the GM Optimality Score (GMOS) at the writhing age [17], and the Motor Optimality Score (MOS) at the fidgety age [26], where a higher score represents more optimal movements. Full explanation of movement criteria is available in previous publications by the GM trust [17, 25] . In a study of 40 extremely preterm infants, 33 infants showed normal fidgety movements, but of

these 33 infants only six were found to have the highest MOS score possible [27], highlighting the increased sensitivity of optimality scoring compared to global GMA.

Should GMs be shown to be an early biomarker for cognitive impairment, there are still barriers to implementing GMA as a population level screening tool. These barriers include access to trained assessors in many locations, and the cost involved in video recording of the infant. To overcome these barriers, a smart-phone app called Baby Moves has been developed allowing families or health professionals to record and upload GM recordings directly and has been successfully utilised for fidgety age assessments on high risk infants [28], removing the need for in-person appointments.

The use of machine based movement recognition, aimed at automatic detection, classification and quality assessments of limb movements has the potential to further reduce the time and financial costs of GM assessments. This approach has been explored by a number of researchers aiming to automate reporting of fidgety GMs in small samples of clinical GM videos [29-34]. Results suggest automated readings of fidgety movements are feasible, reporting sensitivity and specificity of 79-85% and 63-71% respectively [29-31]. The machine learning field is relatively young, and is rapidly evolving and advancing. Through adoption of new techniques, and a large training dataset, it is expected the sensitivity and specificity can be improved [35]. Automated video analysis may provide a low-cost, high sensitivity approach by combining the sensitivity of advanced machine classification (used as a primary screening mechanism), and the specificity of human expert opinion (for any videos classified as high risk by the automation).

It is known that a child's biological and environmental profile is related to developmental outcomes [36-38]. A number of protective and risk factors, particularly birth weight, gender and prematurity, and maternal age are routinely collected and documented. Applying a bioecological model [39] to explore developmental vulnerability using routinely collected data, in conjunction with GM assessments may provide a stronger predictive tool than GM's alone creating a robust and meaningful screening tool [36].

Identification of an early biomarker, along with the development and validation of an accessible affordable and scalable screening tool, for the early identification of

cognitive impairment would allow a greater number of infants to receive effective early interventions during the critical window of brain development: an advantage to the child, family and greater society.

"The economic benefit [of early detection and intervention] could be great, but the benefit to the families is priceless"

-Kids Rehab WA Consumer group member

Aims and Hypothesis

Phase One – GMA as a biomarker

The primary aim of phase one is to determine the diagnostic value of GMs for cognitive delay at two-years.

It is hypothesised that abnormal GMs at either writhing or fidgety age will be predictive of cognitive delay at two years. As this is the first study to look at the predictive ability of GMA for cognitive delay or impairment in a large representative birth cohort, we have insufficient data to hypothesise the diagnostic test accuracy.

The secondary aim of phase one is to develop and refine automated assessment for both writhing and fidgety periods respectively, including optimality scoring, through applying machine based learning to the data. It is hypothesised that automated scoring of GMA will have >90% sensitivity and >85% specificity to detect global GM abnormalities, with lower accuracy for optimality scores.

Phase Two – Screening algorithm

The primary aim of phase two is to develop screening algorithms for identification of children at risk of cognitive impairment, using the GMA, and routinely collected social and environmental profile data.

It is hypothesised an algorithm of early child, family and societal risk factors and GMA and optimality scores, will be a more accurate predictor of cognitive status at 2 years corrected age than GMA or optimality scores alone.

Phase Three – Cost and economic evaluations

The primary aim of phase three is to conduct a cost evaluation for GMA implementation from the perspective of the funder in preparation for national implementation.

The secondary aim of phase three is to assess the relationship between cognitive status and health care utilisation, medical costs, health-related quality of life and caregiver burden.

It is hypothesised cognitive impairment will predict; higher health care utilisation and direct medical costs, poorer health-related quality of life and higher caregiver burden.

Methods

Study Design

This study is a double-masked, prospective cohort study of 3,000 babies. The methodological design of this cohort study has been informed by the 2007 "Strengthening the Reporting of Observational Studies in Epidemiology" (STROBE) checklist for cohort studies [40]. The methodological design of phase one (a study of diagnostic test accuracy), was informed by the 2015 "Standard for Reporting of Diagnostic Accuracy Studies" (STARD) checklist [41].

Setting

Early Moves is a multi-site study, recruiting in secondary care settings in metropolitan Perth, WA. This study is a sub-study of the ORIGINS project, a major Western Australian cohort study of 10,000 families who birth at Joondalup Health Campus, WA, a public/private secondary hospital in Perth's northern suburbs [42, 43]. The ORIGINS project is the largest representative sample of Australian infants in an observational cohort study, and includes a number of optional nested interventional studies. Early Moves will initiate recruitment through the ORIGINS project, before expanding to additional metropolitan secondary hospitals.

Recruitment

Early Moves will recruit a total of 3,000 infants between November 2019 and December 2022. It is anticipated two thirds of participants will be recruited through the ORIGINS project. Recruitment can occur at any time, from initial presentation at antenatal clinic, up until discharge from hospital after the birth of the baby. To reduce

risk of self-selection bias on the basis of birth experience, antenatal recruitment will be targeted where possible (Figure 1). Timing of consent relative to birth will be recorded. Potential participants will be recruited directly by their maternity or postnatal care provider, or by a member of the ORIGINS or Early Moves research team. Recruitment flyers and posters will also be used at study sites. The first 3000 eligible participants who provide informed consent will be enrolled in Early Moves. As all mothers birthing at each site are invited to participate in the study we anticipate the rates of preterm to be similar to that found in the general population at 8.2% [44].

Inclusion Criteria

a) Mother intending on birthing/have recently birthed at a select WA public or private hospital between 2019 and 2023

Exclusion Criteria

a) Babies enrolled in an ORIGINS interventional research study that aims to promote cognitive and language development.

Masking

The assessors will be masked to baby's gestation at birth; birth, medical and social history and the results of any of the ORIGINS or *Early Moves* outcomes. Abnormalities in serial GM assessments are known to be predictive of cerebral palsy, so in cases where abnormalities are identified, the participants will be notified and referred to the appropriate clinical services for further investigation and management. Based on rate of cerebral palsy in Australia of 1.4 per 1000 live births [45], we anticipate to identify approximately 5 cases of cerebral palsy, where parents will be unmasked to GM outcomes as per above protocol.

Bias

As a prospective cohort study selection bias is minimised as participants will enrol prior to or very soon after the birth of the baby. Inhomogeneity of the cohort and exposure to other interventions (interventions that do not meet the exclusion criteria) will be explored as potential biases. , Where available, Ages and Stages Questionnaire [42] (administered as part of the ORIGINS project), will be used to explore study bias for drop out in the *Early Moves* study. Exclusion from *Early Moves*

on the basis of enrolment in an intervention study will be reviewed to explore selection bias relating to risk of neurodevelopmental disorder.

Phase One: Predictive Variables

General Movements will be obtained using the Baby Moves smartphone app. A 3 minute video is taken using the app with the baby lying supine on a plain, flat surface in an awake, settled state, with arms and legs visible. Videos are securely uploaded to the study database for remote assessment by the GM assessors according to Prechtl's GMA, and calculation of GMOS [17, 25] and MOS [25, 26]. The Baby Moves app has been successfully piloted on 446 infants to determine feasibility at the fidgety period [28, 46], with 69.9% - 82.7% of the videos taken by families scorable [46]. This study seeks to reduce the proportion of un-scorable videos to 15% by employing personalised training and parental education, instructional films and the use of e-reminders of upcoming and currently due videos, and phone support. Further, as this study commences with the first video made within 2 weeks post-term rather than 12 weeks post-term, we anticipate families will be more engaged with the study compared with early studies using the Baby Moves app. Videos received will be reviewed within two weeks of submission to check for quality, and families will be contacted via phone if the video is un-scorable. Collection of two videos within each time period further increases the likelihood of one scorable video being attained within each time period.

Remote GMA will be conducted for each of the two time periods, (Figure 1). For the purpose of exploring the predictive ability of GM on cognitive impairment, assessment will be conducted on the first video, with the second video used if a) the first is not scorable, or b) there is uncertainty around classification and further video footage is required to make a final decision.

1. Time-period 1 "Writhing" – videos collected at 1+0 to 2+6 and 3+0 to 4+6 weeks post-term age. Movements will be classified, and GMOS calculated.
2. Time-period 2 "Fidgety" – videos collected at 12+0 to 13+6 and 14+0 to 16 +6 weeks post-term age. Movements will be classified and MOS calculated.

General Movement Fidelity

General Movement Assessments will be conducted by qualified and registered clinicians who have experience in reporting GMA's and have passed the advanced GMs course by the General Movements Trust. The assessors must have experience in clinical and research application of GM assessment prior to involvement in the study.

Each GM and GMOS/MOS assessment will be conducted by two individual assessors. If there is disagreement between the two assessors a third blinded, experienced GM Instructor (ASp or CM), will make the final decision. Disagreement is defined as difference in GM categorical assessment, or optimality scores of more than five point difference [47].

The interrater reliability of the three assessors for GMA will be accepted as "almost perfect" (≥82% of data are reliable, with Cohen's Kappa > 0.9). Interrater reliability and agreement for GMOS and MOS will be accepted as "excellent reliability" (intraclass correlation coefficient of >0.9 using two-way random effects ANOVA) [48]. This will be done by triple scoring the first 10 videos, then 10% (selected at random) of each block of 100 videos until criteria for reliability are met. To ensure reliability is maintained throughout the study, a random selection of 10 videos out of every 300 will be triple scored.

Automated reading of GMA

Advanced machine learning methods have been developed to classify and separate normal versus abnormal videotaped fidgety GM [46, 49]. Video recordings are processed using a pipeline of computer vision and machine learning techniques to predict GMA. Salient point detection (where the joints related to the GM of the infant are located and tracked in the video frames) is followed by extraction of the local motions of the joints into feature vectors. These feature vectors are automatically classified using our anomaly detection algorithm developed during pilot work [49, 50]. Based on a *k* – nearest neighbour classification approach on 265 video recordings of babies, and a feature based on the histogram of the optical flow, the accuracy for automated GMA is 72.9% [50].

Table 1 Source of routinely collected demographic and health factors used for the development of screening algorithms in Phase Two. Factors are grouped according to levels, employing a bioecological model of child development. JHC: Joondalup Health Campus

	Midwives Notification System	JHC Mother's Health Questionnaire
Cultural and Neighbourhood Factors		
Socioeconomic Index (SEIFA)	√	
Ethnicity	√	
Parent/Family Factors		
Marital status	√	√
Smoking during pregnancy	√	√
Alcohol consumption during pregnancy	√	√
Illicit drug use during pregnancy		√
Maternal Medical Conditions	√	
Maternal Mental Health Conditions		√
Perinatal Mental Health Risk Factors	√	
Child/Biological Factors		
Pregnancy complications	√	√
Family History of Developmental Difficulties		√
Method of Birth	√	
Complications of labour and birth	√	
Gender	√	
Infant Weight	√	
Resuscitation	√	
Estimated Gestation	√	
Birth defects	√	
Birth trauma	√	
Special care number of days	√	
Plurality	√	

Phase One: Primary Outcomes

The *Bayley Scales of Infant and Toddler Development* is the most frequently used test in infant developmental assessments [51]. The fourth edition of the scale

(Bayley-4) has recently been released and will be used in this study at age 2 years corrected. The Bayley-4 scores across five subdomains: Cognitive, Language, Motor, Social-Emotional and Adaptive Behaviour. In *Early Moves* the primary outcome will compute a combined cognitive *and* language score calculated as the average of the cognitive score and the language score [52, 53]. Cognitive delay will be defined as severe when cognitive *and* language score is greater than 3 standard deviations (SD) below the Australian mean, moderate when the score is between 2 and 3SD below the Australian mean, and mild when the score is between 1 and 2SD below the Australian mean [54]. Children unable to complete psychological testing because of presumed severe cognitive delay will be assigned a score of -4 SD. Secondary analysis will be conducted on cognitive domain score alone. If babies score <-2SD on the Bayley-4 across any domain, they will be referred to the appropriate developmental services for further investigation and management.

Medicare Benefit Scheme data and health resource use questionnaires will be used to identify participants who have received cognitive interventions as part of their standard clinical care and a sensitivity analysis will be performed to assess the extent to which inclusion of these participants identified as high risk of cognitive impairment impacts the primary results.

Phase Two: Screening Algorithms

Screening algorithms for identifying children requiring early intervention for cognitive delay will be developed using data available from the Joondalup Health Campus (JHC) Mothers Health Questionnaire (routinely administered to all mothers intending to birth a JHC), and the Midwives Notification System (Table 1). Linked data from the Western Australian Register of Developmental Anomalies at age 1 year will be utilised.

Phase Three: Health Economics

Health care resources will be measured and standard cost sources will be used to apply unit costs to resources. Costs will be standardised to a reference year and future costs will be discounted according to standard practice. Resources and associated costs will include GMA and Bayley-4. The cost of GMA will include ongoing cost of the app and labour resources required for assessment of the videos. Data collected on health-related resource use will include screening assessments,

therapy frequency and duration (traditional/alternate), hospital admissions, GP and medical specialist visits, medications and equipment.. Data will be collected via the Health Resource use (HRU) questionnaire [55], supplemented by consented access to individual hospital, Medical Benefits Scheme (MBS) and Pharmaceutical Benefits Scheme (PBS) records.

The *Carer Experience Scale (CES)* will be employed as a measure of caregiver burden. This validated measure of care-related quality of life has six domains (activities, support, assistance, fulfilment, control and relationship with the care recipient) and takes approximately 3 minutes to complete [56]. The Carer Experience Scale is scored from an algorithm derived from preferences of the general population and can be used to value carer outcomes in economic evaluation using index values [56].

Sample Size Estimation

Early Moves is a double masked prospective cohort study and will recruit 3,000 babies. For the primary aim to determine the diagnostic value of abnormal GMs for cognitive delay at two-years, this sample size will be sufficient to establish >78% sensitivity and >83% specificity (alpha 0.05) This calculation assumes 15% of participants have at least mild cognitive delay, the actual sensitivity and specificity are 82.5% and 85% respectively, that 15% of participants drop out at 2-year follow up and that15% of videos are not scorable. For secondary outcomes, there is sufficiently high power to detect even small associations between early GM results and Bayley-4 interval scores at 2years. For example if 80% of children have normal GMs as infants, the study is powered to detect between group (GM normal vs abnormal) differences on the Bayley- 4 (cognitive and language) at 2 years of 3.5 points or greater with 80% power (assuming alpha=0.05, and SD=15 points).

Statistical Analysis

Summary statistics will be described using either mean (standard deviation) or median (25th-75th percentile) for continuous variables, according to distribution, or as frequency (percentage) for categorical variables.

For Phase One, the primary aim will be assessed using standard diagnostic statistics (e.g. sensitivity, specificity, predictive values, and likelihood ratios). The predictive

validity of the GM categorical classification will be established using logistic regression. The diagnostic value of machine learning for identifying GM writhing and fidgety categorical classification will be evaluated by determining the accuracy, precision, recall and area under the curve (AUC) of both automated machine assessment and machine-human hybrid assessment using the entire dataset of videos (n=6000). An algorithm for early diagnosis of cognitive impairment will be developed using logistic regression modelling, using variables from the GMOS/MOS, GMA categorical classification. Variables will be entered using forward selection based on the Wald statistic. Sensitivity and specificity of the regression model, with 95% confidence intervals will be established.

For Phase Two, screening algorithms based on the association between measurements recorded at birth or in infancy (e.g. GM category) and measurements recorded at 2 years will be assessed using linear regression for interval outcome data, logistic regression for binary outcome data, and Poisson regression for count outcome data. Hierarchical mixed-effects models will be used with 'participant' included in the model as a random effect in order to account for the non-independence of observations from the same participant. Motor impairment and known risk factors (prematurity, low birth weight, diagnosis of other developmental or genetic disorder) will be tested as a potentially confounding variable for all models. Variables will be selected for potential inclusion in multivariable models based on univariable significance at the $p<0.2$ level. Multivariable models will be built in a step-wise manner with redundant variables eliminated using Akaike's and Schwarz's Bayesian criteria. Interactions will be investigated as appropriate.

For Phase Three, cost and economic evaluations will consider service use and service costs. We will describe patterns of met and unmet need in the study children, and indirect costs to families will be examined. Associations between costs and all other outcome variables, including those related to cognitive outcome will be assessed, with adjustment for confounders.

Ethics and dissemination

The ORIGINS Project (ref. #1440) and *Early Moves* (ref. #1902) has been approved by the Human Research Ethics Committee of JHC. Participant information booklets

will be provided to all participants prior to entry into the study, and full written and informed consent will be obtained from all participants.

A collaborative (push, pull, exchange) knowledge translation model has been adopted in this study [57, 58]. Project investigators will champion knowledge translation across five levels of Health: Consumer and Service Providers; Department; Program; and Health Service Level. Specific knowledge translation strategies and skill building activities will be targeted across the phases of the *Early Moves* Project, and in consultation with our stakeholders. This will include, but are not limited to, dissemination of findings to consumers and stakeholders via peer reviewed publication of study results, plain language summaries, newsletter feedback and media case studies, as well as presentations at key national and international conferences.

Public/patient involvement

Community engagement is at the core of the ORIGINS and *Early Moves* projects [42], with the implementation of a collaborative model of involvement [59]. Community members of a clinical consumer reference group were involved in the priority setting for the study, specifically parents of children with cognitive impairment. When asked whether they felt the study was important and worthwhile, the response was very positive, e.g. “Yes, yes, yes. I don’t understand why you wouldn’t do it.” The group also endorsed time points, methods for collection of data and follow up protocols for abnormal GMA results. Furthermore, ORIGINS has a dedicated community stakeholder coordinator and 12 parents whom form a consumer reference group. This ORIGINS consumer reference group has been involved in development of recruitment and information and consent materials for *Early Moves*. Consumer and community representation is also incorporated in the ORIGINS and *Early Moves* governance structure.

Bidirectional, effective and continuous communication with consumers will guide research directions, interpretation of findings and their implications for policy.

Discussion

At present, lack of early biomarkers for cognitive impairment hinders referral to early interventions. *Early Moves* aims to identify early biomarkers for babies at risk of

cognitive impairment, allowing early intervention within critical developmental windows to enable babies to have the best possible start to life.

The study has a number of strengths. It is a well powered study with a population-based sample. Where possible, participants will be recruited during the antenatal period to minimise self-selection bias where it relates to the birth experience (e.g. prematurity; late pregnancy or birth complications). The assessment variables utilised in this study have proven reliability and validity. As a sub-project of the ORIGINS project, *Early Moves* will have access to biobank data, to generate a detailed biological and environmental risk profile, to inform predictive algorithms, and investigate links between cognitive impairment and biological and environmental factors. The study has strong consumer involvement and an embedded knowledge translation plan which will help guide and facilitate the translation of research findings in to clinical practice.

A potential limitation is that the final outcome measure is conducted at two years. Research in premature babies shows the association between abnormal GMs and cognitive impairment is weaker at 2 years compared to 4 years [24]. A subset of the cohort will however be followed until age 5 years as part of the ORIGINS project, with later assessments to include developmental assessments such as Ages and Stages questionnaires and linkage to the Australian Early Development Census (AEDC) providing data on early childhood development at entry to the first year of full time school. The AEDC is an Australian wide data collection conducted by teachers using the Australian version of the Early Development Instrument. . This study is also potentially limited by recruitment at greater metropolitan sites within one Australian city. Demographic data will be available to aid in the interpretation of generalisability to other populations.

Early Moves will provide novel care models in rural and remote communities through the use of smart phone technology and machine based learning, facilitating the feasibility of app-based GM assessments as a population wide assessment tool. Through combining automated app-based GM assessments with routinely collected risk and protective factors, employing a bioecological model of development, *Early Moves* recognizes the complex interplays of risk and protective factors to create a robust screening tool for cognitive impairment in infants. Inclusion of health

economics evaluation will further enhance the potential for this technology to be translated in to clinical care.

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Conflict of Interest

None declared.

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Author Contributions

CE and JV are the chief investigators and together with CA, ASa, ASp, RNB, NB, CM, DS, EG, and RSW designed established and achieved funding for the research study. AA, AM, DB, MS, RW, SB, SP, SW, VL, SD, AT, LJ, NA, and the Early Moves Clinical Working Party also contributed to study design. CE, JV and CA are responsible for ethics applications and reporting. CA, DS, and SP are responsible for recruitment. CE, JV, CA, ASa supervise the data collection and implementation of training. CE, JV, ASa, AS, CM, MS, NA and the Early Moves Clinical Working Party are responsible for design and implementation of GM outcomes. NB, CM and VL are responsible for design and implementation of machine learning outcomes. AT, AM, RW, SD and AA are responsible for design and implementation of consumer engagement outcomes. EG and AFJ are responsible for design and implementation of health economics outcomes. SW, DS and CA are responsible for design and implementation of routinely collected screening outcomes. JV, ASa, and SB are responsible for design and implementation of developmental outcomes. CE, JV, CA, ASa, ASp, RNB, NB, CM, DS, EG, and RSW will take lead roles in preparation for

publications on the clinical outcomes of the study. RSW will take on a lead role of statistical analysis for the study. All authors contributed to the preparation of this manuscript and have approved the final version.

Data statement

De-identified individual participant data that underlie the results published in articles resulting from this study will be made available to researchers on a case by case basis, beginning 6 months and ending 5 years following the relevant article publication. Data will be made available to researchers who provide a methodologically sound proposal with appropriate research governance and ethics approvals, for the purposes of achieving aims of approved proposal of for use in meta-analysis. Proposals should be directed to Catherine Elliott OCRID ID: https://orcid.org/0000-0002-5324-8216

Figure 1: Study assessment timeline

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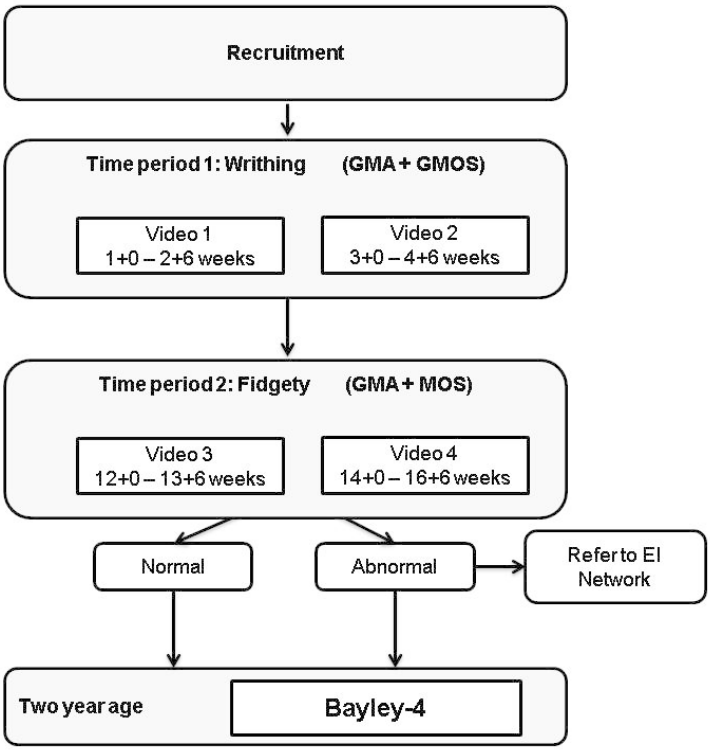

Caption : Study assessment timeline. GMA: General Movement Assessment. GMOS: General Movement Optimality Score. MOS: Motor Optimality Score. EI: Early Intervention

190x300mm (96 x 96 DPI)