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Harnessing neuroplasticity to improve motor performance in infants with cerebral palsy: a study protocol for the GAME randomised controlled trial

Catherine Morgan [iD] ,[1] Nadia Badawi,[1,2] Roslyn N Boyd,[3] Alicia J Spittle [iD] ,[4] Russell C Dale,[5] Adrienne Kirby,[6] Rod W Hunt,[7,8] Koa Whittingham [iD] ,[9,10] Kerstin Pannek,[11] Rachael L Morton,[6] William Tarnow-Mordi,[12] Michael C Fahey,[7] Karen Walker,[13,14] Kristina Prelog,[15] Catherine Elliott,[16,17] Jane Valentine,[18] Andrea Guzzetta,[19,20] Shannon Olivey,[8] the GAME study team, Iona Novak[21,22]

For numbered affiliations see end of article.

Correspondence to
Dr Catherine Morgan;
cmorgan@cerebralpalsy.org.au

ABSTRACT

Introduction Cerebral palsy (CP) is the most common physical disability of childhood worldwide. Historically the diagnosis was made between 12 and 24 months, meaning data about effective early interventions to improve motor outcomes are scant. In high-income countries, two in three children will walk. This evaluator-blinded randomised controlled trial will investigate the efficacy of an early and sustained Goals–Activity–Motor Enrichment approach to improve motor and cognitive skills in infants with suspected or confirmed CP.

Methods and analysis Participants will be recruited from neonatal intensive care units and the community in Australia across four states. To be eligible for inclusion infants will be aged 3–6.5 months corrected for prematurity and have a diagnosis of CP or 'high risk of CP' according to the International Clinical Practice Guideline criteria. Eligible participants whose caregivers consent will be randomly allocated to receive usual care or weekly sessions at home from a GAME-trained study physiotherapist or occupational therapist, paired with a daily home programme, until age 2. The study requires 150 participants per group to detect a 0.5 SD difference in motor skills at 2 years of age, measured by the Peabody Developmental Motor Scales-2. Secondary outcomes include gross motor function, cognition, functional independence, social–emotional development and quality of life. A within-trial economic evaluation is also planned.

Ethics and dissemination Ethical approval was obtained from the Sydney Children's Hospital Network Human Ethics Committee in April 2017 (ref number HREC/17/SCHN/37). Outcomes will be disseminated through peer-reviewed journal publications, presentations at international conferences and consumer websites.

Trial registration number ACTRN12617000006347.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Largest randomised-controlled trial in infants with or at high risk of cerebral palsy (CP) ever conducted.
⇒ Participants are infants identified with or at high-risk of CP using international guidelines.
⇒ Outcomes include motor function, cognition, social–emotional well-being and quality of life.
⇒ A health economics analysis will assess the cost-effectiveness of the intervention compared with usual care.
⇒ Usual care intervention is variable.

INTRODUCTION

Cerebral palsy (CP) is the most common childhood physical disability.[1] CP is life-long, worsens health, includes early-onset ageing, with low likelihood of employment.[2,3] Among children with CP a systematic review indicates 3 in 4 experience chronic pain; 1 in 3 cannot walk; 1 in 3 have a hip displacement; 1 in 4 cannot talk; 1 in 4 have epilepsy; 1 in 4 have a behaviour disorder; 1 in 5 have a sleep disorder; and 1 in 10 are blind.[4] The condition has five levels of functional severity (ambulant to wheelchair dependent)[5] and no single rehabilitation treatment yet exists to lessen the severity.

Despite universal beliefs about the benefits of early intervention, systematic reviews[6,7] indicate that traditional early intervention is ineffective for infants with CP, with most trials failing to confer any motor gains.[6] Significant shortcomings exist within standard early intervention for infants with CP and research studies to date in that: (1) intervention is late, not early due to delayed diagnosis[8]; (2) many traditional therapy approaches involve hands-on therapist-executed movements, where the infant's role in movement generation is passive not active, all of which have been proven ineffective and fail to harness neural plasticity[7,9]; (3) intervention is under-dosed[10]; and (4) major methodological flaws

exist in previous trials. In addition, early identification of risk for CP was historically less accurate leading to inadvertently recruiting and treating normal infants within CP trials, reducing statistical power.[6]

Late versus early intervention

Staggeringly only 50% of infants with CP get any intervention before 12 months of age.[11] The convention has been to 'wait and see' if motor delay persists until 2 years,[11] whereas neuroscience suggests intensive intervention involving child-activation of their motor circuitry should occur early. Population data show CP gross motor performance plateaus and is less responsive to motor treatment after 3.5–5 years of age because 90% of motor potential is reached.[12] Thus, late intervention likely limits optimal motor outcomes because almost the entire neuroplastic window for motor learning is missed.[8 11] In addition, without early intervention, deterioration and maladaptive neural plasticity occurs. Preclinical data show that neural circuits not actively engaged in tasks degrade,[13] providing biological evidence that late intervention is detrimental to the motor circuitry of infants with CP. Swedish CP population data confirm that children who do not receive regular early interventions have substantially worse musculoskeletal deformities (<1% hip dislocations in early-treated[14] vs 30% in untreated or late-treated,[4] and higher rates of contractures and scoliosis). Late intervention may allow the formation of compensatory behaviours producing maladaptive neural and muscle plasticity,[15] culminating in the onset of secondary musculoskeletal deformities, which impede the effect of late training.[13]

Low dose versus high dose training

A survey of early intervention providers revealed infants with CP received as little as 14 hours of rehabilitation in the first year of life,[10] the same dose that adults are recommended to receive in the first 2 weeks post-stroke.[16] It is now known in older children with CP, that the threshold dose of intervention is 14 hours per goal task,[17] and infants have multiple goal tasks to learn (eg, sitting, standing, walking, grasping toys, etc) suggesting a high dose of training will be required.

Usual care approaches

When usual care eventually starts it is often not evidence-based, as it typically involves traditional passive movement approaches, which have been proven ineffective.[7 9] Neuroscience preclinical data strongly support early active movement training as an intervention for improving brain reorganisation and outcomes after early brain damage. In preclinical studies, training induces reactive synaptic plasticity, dendritic growth and synaptogenesis; increased cortical territory dedicated to the trained skill; lasting changes in synaptic strength and numbers, corresponding to motor map reorganisation; elevation of neurotrophic factors and other plasticity-related processes improving functional outcomes; and sparing of neuron death and lost connections after brain injury.[13] In the feline model

of CP, early training restores corticospinal tract connections and the primary motor map, plus improves functional motor performance. In contrast, late training has no impact on motor function even though tract connectivity is established.[18] The feline model also suggests that early training must occur before corticospinal tract development and reorganisation completes at the equivalent of 6 months of age in humans to be effective.[18]

Other commonly used approaches include a developmental skills paradigm where a structured curriculum across multiple developmental domains is applied similarly across many types of disability, resulting in generic intervention.[19] In contrast, our Early Intervention International Clinical Guideline[20] based on systematic reviews and high-quality RCTs, outlines recommendations for a child-active motor and cognitive training approach which is both context and task specific, starts early and involves parents as key partners in delivering a sufficient dose of practice.

Our earlier systematic review[7] of the state of the evidence for CP interventions found that effective interventions included key neuroplasticity modifiers: intensity, specificity, repetition, timing, variability, saliency, enjoyment and challenge.[7 13] RCTs[21 22] also suggest that improvements are even better when training occurs at home. Children learn best in natural settings, where training is personalised to their enjoyment—translating to more intense, specific practice. However, these CP training RCTs[7] were all conducted in children aged 2–18, after the peak of infant neural plasticity, in the less responsive chronic brain injury phase. Neuroscientists hypothesise that the impact of early training on neuroplasticity in infants with CP will produce superior results to those achieved in older children and adults. MRI work[23] confirms that children with CP have cortical plasticity that can be harnessed. Furthermore, our systematic review of environmental enrichment in infants with CP showed that enrichment combined with motor training has a small additive effect on motor outcomes (standardised mean difference: 0.39; 95% CI: 0.05 to 0.72).[24] The ultimate goal of rehabilitation is to induce neuroplasticity that maximises the potential of the injured brain.

We designed a new intervention for infants with CP that was provided early, at high dose, for a sustained duration, using child-active motor and cognitive training within an enriched home environment to harness neuroplasticity, known as 'GAME' (Goals–Activity–Motor Enrichment). This is the largest study ever conducted of an early intervention for infants with or at high risk of CP, addressing the known limitations of usual care.

OBJECTIVES
Primary objective

The primary hypothesis of this study is at 2 years of age compared with usual care, GAME (1 hour weekly therapy plus daily home programme repetition until 2 years of age) will increase gross and fine motor skill total score on

the Peabody Developmental Motor Skills (PDMS-2) by a difference of 7.5 in total motor quotient, equivalent to an increase of 0.5 SD.

Secondary objectives

Secondary objectives are to determine the effects of GAME versus usual care, at 2 years of age on motor capacity, cognitive skills, social–emotional skills, independence in daily living, health-related quality of life; and health costs. An additional tertiary objective is to determine the effects of GAME versus usual care on brain structure and microstructure, for a small proportion of infants who have a 2-year MRI.

METHODS AND ANALYSIS
Design

A phase III randomised controlled trial (RCT) will be conducted among 300 infants with CP or at high risk of CP to evaluate the effects GAME versus usual care. This trial has been designed according to the Standard Protocol Items: Recommendations for Interventional Trials statement[25] and study outcomes will be reported according to the Standard Protocol Items: Recommendations for Interventional Trials statement.[26] The economic evaluation will be reported according to the Consolidated Health Economic Evaluation Reporting Standards checklist.[27] Figure 1 outlines the study design. All infant participants' parents will give written informed consent prior to randomisation. The study is registered on the Australia New Zealand Clinical Trials Register ACTRN12617000006347.

Participants
Inclusion criteria

Participants identified in the neonatal intensive care unit (NICU) or community will be eligible if they fulfil the following criteria:
1. Aged 3–6.5 months (corrected for prematurity)
2. Discharged home from hospital.
3. Diagnosis of CP OR diagnosis of 'high risk of CP' according to the International Clinical Guideline for Accurate Early Detection[8] with either: (1) General Movements 'Absent fidgety' score+abnormal brain MRI/CUS indicating risk for motor impairment; OR (2) General Movements 'Absent fidgety' score+Hammersmith Infant Neurological Evaluation (HINE) score <57 at 12 weeks/<59 at 26 weeks of age; OR (3) Abnormal brain MRI/CUS indicating CP+HINE <57 at 3 months of age/<59 at 6 months of age. (Where infants have evidence of unilateral injury and clinical asymmetry indicating hemiplegia, HINE scores >57 will be accepted as per literature.[28]) Available neuroimaging will be assessed for eligibility by a paediatric neurologist or neonatologist masked to the infant's clinical history.
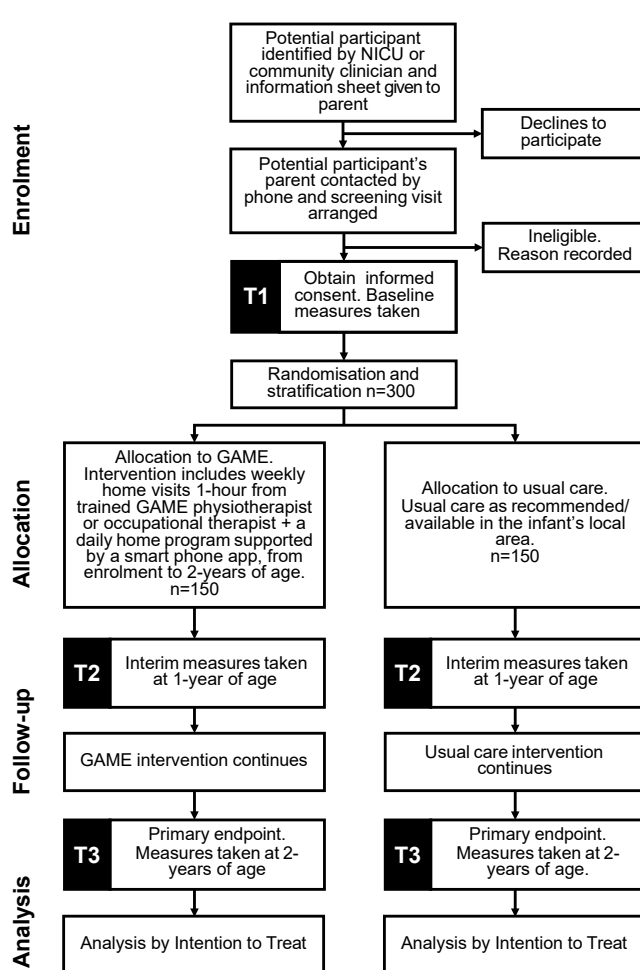

Figure 1 Study diagram. GAME, Goals–Activity–Motor Enrichment; NICU, neonatal intensive care unit.

Exclusion criteria

1. Drug-resistant epilepsy meeting the International League Against Epilepsy criteria.
2. Severe vision impairment (unable to fix and follow in good light).
3. Medically fragile preventing safe child-active participation in training.
4. Living in remote location inaccessible by study personnel for home visits.

Recruitment

Families with an infant or infants potentially meeting eligibility will be invited to be screened for the study from our current network of 11 collaborating centres, across 26 sites, of therapists, neurologists, paediatricians and neonatologists in the four Australian states (New South Wales (NSW), Queensland (QLD), Victoria (VIC), Western Australia (WA)). Investigators (including the parent investigator) or a physician, nurse or allied health professional will provide a potential participant with an information sheet during NICU and Special Care admissions and/or during therapy or follow-up clinics. After consent to share information, professionals will be able to refer and/or parents will be able to initiate screening by

providing or consenting to researchers taking a video of their infant's general movements. Parents who voluntarily upload videos will then be met by investigators face-to-face to discuss assessment results, their infant's risk for CP and eligibility for study enrolment. Potentially eligible participants will then be given a screening appointment with the study physiotherapist or occupational therapist at the infant's home or as an outpatient to conduct any screening assessments not available in their history or data upload. Screening will only occur once the infant reaches 3 months of age (corrected for prematurity). If eligible, the family will have an opportunity to have any questions answered, before informed consent to enrolment. Data collection for the GAME trial commenced in June 2017 and is anticipated to be completed in June 2023.

Allocation, randomisation and stratification

Randomisation will be performed by using an interactive voice response system (IVRS) built by an independent statistician at the National Health and Medical Research Council Clinical Trials Centre, at The University of Sydney. Randomisation will be by the method of minimisation with two strata: state (NSW, QLD, VIC, WA) and by the severity of neurological examination score defined using the HINE at baseline. A HINE score <40 is regarded as a severe impairment (predicted to be non-ambulant), while a score ≥40 is regarded as a mild–moderate impairment (predicted to be ambulant). After the screening assessment, consent and baseline measures are taken, the study therapist will call the IVRS and notify the family and study coordinator of the infant's group allocation.

Blinding

All outcome assessors will be masked to group allocation. The statistician conducting the primary data analysis will also be masked to group allocation. The participants and the study physiotherapists and occupational therapists delivering the intervention cannot be masked to group allocation due to the nature of the intervention being tested.

Interventions

GAME is an early training intervention informed by dynamical systems theory,[29] and perception–action theory.[30 31] In these compatible frameworks infant learning and development occurs through an ongoing cycle of perception followed by an action which in turn influences perception as the infant learns how to extract and purposefully use information from their environment. GAME intervention fundamentally enriches the infant's natural environment to provide variable learning opportunities for learning and applies neuroplasticity principles including intensity, salience and repetition,[32] and motor learning principles of distributed practice with attention to both intrinsic and extrinsic feedback.

Our pilot studies confirmed from objective logbook data that GAME is novel and different to usual care in

rationale, content, materials and mode of delivery[10 33–35] (table 1).

Essential active ingredients of GAME intervention include
GAME motor training

Motor goals (eg, independent sitting) are first set by parents and then the therapist identifies and explains to families the factors limiting goal performance (eg, poor motor control). Training is then designed to target goal achievement. Training is goal-oriented and play based, customised, task and context-specific, providing the necessary repetition (with attention to frequency and duration) required to learn to perform the new goal behaviours independently. Motor training is conducted at the limit of the infant's performance ability with variation and incremental increasing complexity built into task practice. Emphasis is placed on infant-generated active motor learning.

GAME parent coaching in motor training

Parents are coached to provide motor training and cognitive stimulation within their child's natural playtime. Coaching involves helping parents learn to identify their child's voluntary attempts to move and how to enrich and adapt motor activities to motivate their child to move more. They are educated about usual developmental trajectories and how to advance progress. Coaching is embedded within a parent responsiveness framework and support is given to optimise parent mental health, empowerment and emotional availability. Extra parent support is provided when emotional availability or mental health issues are identified.[36] Coaching is customised to the family's culture, education, and parenting preferences.

GAME environmental enrichment

Early interventions using environmental enrichment strategies in the motor, cognitive, sensory and social domains are applied to advance motor development.[24] GAME is provided in the natural home environment where training is personalised to the infant's enjoyment and family customs—translating to more intense, specific and relevant practice. GAME intervention enriches the: (1) *physical environment* by setting up spaces within the home with activities and materials selected to entice infant-generated motor practice at the appropriate level of challenge; (2) *cognitive environment* by encouraging infant problem-solving and self-correction of errors plus reading to children in an interactive manner which has been proven to advance IQ[37]; (3) *sensory environment* by providing evidence-based interventions that improve backdrop capacity for learning, including: pain management, feeding interventions that ensure adequate nutrition for attention[37] and sleep management that produces a wakeful state for learning; and (4) *social environment* by coaching parents to be sensitive, responsive and communicative to infant cues,[36] and promote their child's involvement in family events and routines.

Table 1 TIDieR checklist—how GAME is different to usual care

Item	Experimental group	Control group
Name	Goals, activity, motor enrichment	Usual care early intervention
Why	Rationale: Early, intense, motor learning training induces activity dependent neuroplasticity. Outcomes are enhanced when training occurs within the infant's enriched home Essential elements: ▶ Task specific motor training ▶ Parent coaching in motor training and ▶ Environmental enrichment ▶ Movement actively practiced by the infant with their parent as coach	Rationale: Motor skills innately emerge in a pre-set developmental order. Passive experiences of normal movement and symmetry are applied by the therapist to normalise and correct movement Essential Elements: ▶ Developmental approach ▶ Neurodevelopmental therapy ▶ Adaptive equipment ▶ Movement often passively experienced by the infant from their therapist
Materials	Enriched play environments with novel and carefully selected toys are set-up to entice infants to actively, intensely and repeatedly practice and persist with problem solving demanding motor tasks until independence/goal attainment is reached Minimal use of adaptive equipment	Therapist physically facilitates the infants to passively experience normal movement patterns Adaptive equipment is used to compensate for tasks the infant cannot perform
Who	Infant and parent coached by physiotherapist+occupational therapist	Physiotherapist and/or occupational therapist to the infant and parent education
How	Home based, enriched naturalistic setting	Clinic or hospital-based Intermittent home visits
How much	Weekly GAME trained therapist-provided + Daily parent-provided	Weekly–monthly therapist-provided + Daily parent-provided
Tailoring	Tailored to infant's brain injury, motor severity, cognition, preferences, family goals, parent skills, and own home environment	Variable Typically, generic intervention and developmental stimulus ideas (eg, tummy time) are provided to all infants
How well	Only the GAME therapists will be educated in GAME. Fidelity checks will be conducted by the study investigators using a fidelity measure	Families of usual care participants will be surveyed about intervention approaches used

GAME, Goals–Activity–Motor Enrichment.

GAME dosage

A central tenet of GAME is to achieve daily practice of goals in a way that is enjoyable and feasible for the infant and parent. The GAME protocol includes both therapist-delivered and parent-delivered intervention. *Therapist-delivered intervention:* GAME trained physiotherapists and occupational therapists will provide a weekly 1-hour face-to-face home visit to infants allocated to the GAME group, usually on an alternating basis. In the pandemic, a weekly 1-hour telehealth appointment will be provided instead of a home visit, in compliance with governmental infection control rules at the time and location. *Parent-delivered intervention:* GAME includes home programmes focused on parent-set goals per our previously published intervention protocol and successful clinical trials in the CP population.[33 34 38] The Canadian Occupational Performance Measure (COPM)[39] will be used to frame goal setting conversations and re-evaluated every 3–4 months to ensure the outcomes meaningful to the family are captured. In the GAME group the content of the home programme and a dosage log is provided on a password-protected GAME smart phone app that is loaded onto the parent's personal phone (figure 2). The user's content will be individualised to reflect the parent-set goals, the child's ability and the family home environment, coupled with photographs of the actual participant engaging in the target practice in their home, to support parents with lower written literacy levels. The GAME home programme will be updated regularly to reflect current practice targets. The app will also be provided in the control group, but functionality will be limited to only dose recordings.

GAME infants will be able to access any other early intervention they choose on top of GAME. Parents will be asked to keep a record of all therapy accessed.

Therapist training

Physiotherapists and occupational therapists with more than 3 years working with paediatric or neurological populations will be trained by the first and senior authors over 2 days in the study intervention protocol. After training each therapist will apply the protocol in one infant and present the assessment and intervention carried out as a case study to the trainers and other GAME team therapists for full certification. Therapists are provided with a specific GAME manual and access to a bank of suggested activities which can be used throughout the study period. Therapists are encouraged to develop customised home programmes with their own or parent's ideas also included.

Baseline and outcome measures

Extensive baseline demographic data will be collected including information about the infant's birth, NICU
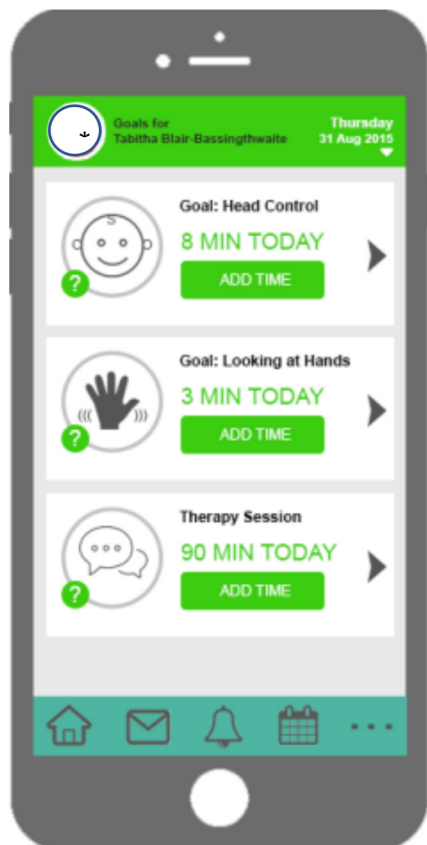
Figure 2 GAME study home programme app. *Demonstration/sample only. GAME: Goals–Activity–Motor Enrichment.

stays, neuroimaging results and associated health conditions for example, sensory impairments. Demographic data about household structure, income, employment and parent education will be collected at baseline and updated at T2 and T3. Clinical MRIs collected in the neonatal period will be blind scored by a paediatric neurologist, neuroradiologist and/or neonatologist and categorised according to the MRI Classification Scale for CP.[40] All of the outcome measures and their psychometric properties and measurement time points are summarised in table 2. Three measurement time points will be taken: baseline (T1); interim measures at 1 year of age (T2); study completion primary endpoint at 2 years of age (T3).

Primary outcome
Motor: Peabody Developmental Motor Scales version 2 (PDMS-2)
The PDMS-2 is the primary outcome measure in this trial and is a frequently used assessment of gross and fine motor skills, combined to produce a total motor quotient (TMQ). This test is standardised and norm referenced for children aged from birth to 6 years and has been validated as a discriminative measure. Two studies have demonstrated that it is responsive to change in the CP population for infants and toddlers when the change in raw scores is considered.[41 42] We will therefore analyse both the TMQ and the raw scores. It has demonstrated concurrent validity with the Gross Motor Function Measure (GMFM)[43] and the Bayley Scales of Infant and Toddler Development (BSITD-III).[44] Assessments will be scored from video by a masked assessor.

Secondary outcomes
Motor capacity: GMFM-66
The GMFM is a criterion-referenced tool that is widely accepted as the gold standard for gross motor assessment in children with CP.[45] The test is valid, reliable and responsive to change in this population. A total of five dimensions are measured: rolling, sitting, crawling, standing and walking/running/jumping. The GMFM-66 version of this instrument will be used. Infants will be videoed at all time points during the assessment and a masked assessor will score from the video according to the test manual.

Cognition: Bayley Scales of Infant and Toddler Development, third edition (BSITD-III)
The BSITD-III is a standardised and norm-referenced assessment, which measures the cognitive, motor, language and social–emotional development of infants and toddlers aged 0–3.[46] Only the cognitive domain will be used at 12 and 24 months. Masked assessors will conduct the assessment in person where possible, or a video will be taken during the assessment and scored by a separate (masked) assessor.

Independence in activities of daily living: Paediatric Evaluation of Disability Inventory Computerised Assessment Test (PEDI-CAT)
The PEDI-CAT is a standardised, norm-referenced assessment of independence and levels of assistance required in self-care, mobility and social function.[47] The test is valid, reliable and responsive in children with CP. Parents self-report the child's independence on an iPad application. The test has an item bank refined using Rasch on large samples of normal and physically disabled children, which intuitively lowers the number of test items the parent must complete, dependent on the child's scores.

Quality of life: the Infant Toddler Quality of Life Questionnaire (ITQOL)
The ITQOL was developed for use in infants and toddlers at least 2 months of age up to 5 years.[48] The ITQOL measures quality of life across physical, mental and social well-being. The test has 97 items in the short-form and is completed by parent report. For each of the 97 questions, item responses are scored, summed and transformed to a scale from 0 (worst health) to 100 (best health). We will report 10 domains following selected norms, including norms for males and females at 2–12 months, 12–23 months, 24–35 months, norms for acute health illness, no chronic, one chronic, more than two chronic conditions, norms for first born infants and norms for infants requiring a NICU stay.

Behaviour: the Infant Toddler Social Emotional Assessment (ITSEA)
The ITSEA is a parent-report checklist of the child's adaptive behaviours (eg, attention, ability to sleep).[49] These behavioural challenges are known comorbidities with CP.

Table 2 Measures purposes, properties and timepoints

	Domain	Measure	Psychometric properties				Timepoints		
			Valid	Reliable	Responsive	Predictive	T1	T2	T3
Inclusion	Diagnosis	GMs	√	√	N/A	√	√	N/A	N/A
		MRI (term equivalent age)	√	√	N/A	√	√	N/A	N/A
		HINE	√	√	N/A	√	√	√	√
Covariates	Severity	GMFCS	√	√	N/A	N/A	N/A	N/A	√
		MRI (term equivalent age)	√	√	N/A	N/A	√	N/A	N/A
		HINE	√	√	N/A	N/A	√	√	√
	Mental health	DASS-21 (parent)	√	√	N/A	N/A	√	√	√
	Dosage	Time in minutes	N/A	N/A	N/A	N/A		√	√
Primary outcome	Motor	PDMS-2	√	√	√	N/A	√	√	√
Secondary outcomes	Motor capacity	GMFM-66	√	√	√	N/A	√	√	√
	Cognition	BSITD-III	√	√	-	N/A		√	√
	Independence ADL	PEDI-CAT	√	√	√	N/A		√	√
	Quality of life	ITQOL	√	√	-	N/A	√	√	√
	Social emotional	ITSEA	N/A	√	√	N/A		√	√
	Neuroplasticity	MRI (structural and diffusion)	√	√	√	N/A	N/A	N/A	√
Economic evaluation	Costs	Income and employment					√	√	√
		Medicare MBS, PBS, NDIS							√
		ICER					N/A	N/A	N/A

ADL, Activities of Daily Living; BSITD-III, Bayley Scales Infant Toddler Development III; DASS-21, Depression Anxiety Stress Scale 21 items; GMFCS, Gross Motor Function Classification System; GMFM, Gross Motor Function Measure; GMs, General Movements; HINE, Hammersmith Infant Neurological Evaluation; ICER, Incremental Cost Effectiveness Ratio; ITQOL, The Infant Toddler Quality of Life Questionnaire; ITSEA, Infant Toddler Social Emotional Assessment; MBS, Medical Benefits Scheme; MRI, MRI Resonance Imaging; MRI, Medical Resonance Imaging; N/A, Not Applicable; NDIS, National Disability Insurance Scheme; PBS, Pharmaceutical Benefits Scheme; PEDI-CAT, Paediatric Evaluation of Disability Inventory Computerised Assessment Tool; T1, Timepoint 1; T2, Timepoint 2; T3, Timepoint 3.

In previous trials, the ITSEA is responsive to improvements from home-based parent–infant intervention. Four domains are assessed including internalising behaviours, externalising behaviours, dysregulation and competence.

Neuroplasticity: MRI
Where safe and feasible, MRI will be acquired on 3T scanners, at 2 years of age. The 2-year scan is optional and additional parental consent will be obtained at the time of the scan since the MRI will be acquired under general anaesthesia.

Along with standard radiological images, we will acquire high-resolution structural images and multi-shell high angular resolution diffusion-weighted images (HARDI; R1, R2). Structural images will be used to investigate cortical thickness and folding, sulcal depth, deep grey matter volumes and ventricular shape. Diffusion-weighted images will be used to assess brain microstructure using standard diffusion tensor metrics (fractional anisotropy, mean diffusivity) in regions and connections of interest (eg, posterior limb of internal capsule, corpus callosum, corticospinal tract). The relationship between MRI measures (structural and diffusion) and motor skills will be investigated.

Economic evaluation
The economic evaluation addresses the question: From a societal perspective, is the GAME intervention for newly diagnosed infants with CP less than 6 months of age cost-effective at 24 months compared with usual early care interventions? The economic outcomes include improvement in fine and gross motor skills as measured by the Total Motor Quotient of the PDMS-2 scale; and improvement in the ITQOL for overall health, and each domain separately.

Consistent with a societal perspective, all relevant resource use and costs will be identified, measured and valued. This includes health system costs, disability costs

(to the National Disability Insurance Scheme (NDIS) and other providers like Better Start), social services and out-of-pocket costs to families. These will be tabulated separately. Examples of relevant expenses include the cost of delivering the intervention and cost of usual care; outpatient costs (eg, doctor and allied health visits); inpatient hospitalisations and emergency department presentations; prescribed medicines; costs borne by the NDIS and other disability providers; social services (eg, carer's allowances); and out of pocket costs for example, specialised toys or home modifications purchased by families. Resource use will be measured using linked Medicare data (Medical Benefits Scheme and Pharmaceutical Benefits Scheme), and additionally by participant questionnaires in study case report forms. Unit pricing will be obtained from Medicare records, Australian-Refined Diagnosis Related Groups and/or the net efficient price where activity-based funding models are used, and presented in the most recent reference year (eg, 2020), Australian dollars. Costs and outcomes will be discounted by 5% in year 2, consistent with Australian Government recommendations.[50]

For each outcome, the incremental cost effectiveness ratio of the GAME intervention vs usual care will be calculated, and reported with 95% CIs, obtained through non-parametric bootstrapping.[51] Scenario analyses for the cost-effectiveness of GAME will be undertaken for each of the pre-defined stratification factors: that is, state (NSW, VIC, QLD, WA) due to differences in CP service provision and costs; and severity, dichotomised by the HINE score at baseline (<40 vs ≥ 40).

Treatment fidelity
Intervention adherence
The degree to which GAME-trained therapists implemented GAME as intended by the GAME developers, will be evaluated via a home visit from one of the two GAME developers. We will measure implementation adherence against a GAME fidelity checklist, which examines the three essential active ingredients of GAME: (1) motor training, using the Motor Learning Strategy Rating Instrument[52]; (2) parent coaching using the Home Visit Coaching fidelity checklist[53]; and (3) environmental environment using an investigator designed fidelity checklist based on critical elements identified in our meta-analysis.[23] For each GAME participant and study therapist, at least one home visit will be conducted and scored from direct observations of a GAME treatment session. For fidelity to be considered satisfactory, adherence will be expected to be 80% or higher, as per conventional adherence benchmarks.[54] In addition, the same CIs will randomly check COPM progress and home programmes via the GAME study app.

Dose
The dose of intervention will be recorded by parents on a GAME study smartphone app. Parents will record therapist-delivered intervention in minutes (ie, time spent in sessions provided by an allied health professional), and parent-delivered intervention in minutes (home programme time). Regular monthly data entry checks will be conducted. Where data are consistently missing, the study therapists will interview the families for a historical report and assist them to record these data. For families with no mobile phone or internet access, paper logbooks will be provided and collected regularly.

Data integrity
Trial data integrity will be monitored regularly by examining data entry for missing data and errors. All data will be double-checked, with inconsistencies explored and resolved. Data will be cleaned and prepared for analysis by an unblinded statistician, then transferred to the blinded statistician for analysis.

An independent data safety monitoring committee will be constituted to review any adverse events if they arise.

Sample size calculations
A 7.5 difference in TMQ equates to an improvement of 0.5 of a SD on PDMS-2 test scores and is considered clinically meaningful improvement. We achieved this difference in our GAME pilot studies.[10 32] A sample of 180 infants (90 per arm) yields >80% power, with significance set at a two-sided p value of 0.05, to show a difference in motor skills of 7.5 in TMQ with a SD 15.0 (Test TMQ mean=100; SD=15) allowing for 10% cross-overs and 10% loss to follow-up. We have further increased the sample size to 300 infants (150 per arm) to account for any tapering in the rate of motor improvements between 1 and 2 years of age, which has not previously been studied.

Statistical analysis
The data will be analysed by a statistician masked to group allocation. All participants who were randomised to the study and have completed a minimum of one session of either intervention or usual care will be included in the analysis utilising the principle of intention to treat. Analysis will be performed using SPSS (V.25), STATA (STATA, V.15, StataCorp, College Station, Texas, USA) and SAS V.9.4 (SAS Institute).

Statistical significance will be set at $p<0.05$. All tests will be two tailed with point estimates and 95% CIs reported.

The effect of GAME treatment will be analysed separately for each outcome to compare the adjusted difference in means or proportions between the GAME and usual care groups. The baseline characteristics of the two groups will be summarised using frequencies and percentages for categorical variables, mean and SD or median and IQR where appropriate for continuous variables. The proportion with missing values will be given for each variable. Standard analysis of covariance controlling for baseline severity on the HINE and adjusting for stratification by state will be used for normally distributed variables. The effect of GAME will be reported using the mean difference and 95% CI for the TMQ and raw score change. For the secondary outcomes, analyses over

time using a mixed model with random effects will be conducted adjusting for stratification variables. A treatment by time interaction will be included in the model for all analyses, including a time effect. If no interaction exists based on the p value the interaction term will be removed from the model, and reporting will use mean difference and 95% CI. Models will also be created to assess the effect of the following covariates: physical disability severity (Gross Motor Function Classification System scores); parental mental health status (DASS-21 scores); and the relationship between dosage (intervention time in minutes) and outcome. We will also examine the difference in effect by socioeconomic status, parental education level, gestational age and severity of physical disability. We also plan to conduct an exploratory analysis of a disability score, and a post-hoc analysis using the validated multicomponent Global Statistical Test. No imputation for missing data will be done in the primary analysis. A sensitivity analysis will be performed using multiple imputation.

Participants will be provided with their own results on request. After the final results are published, the overall deidentified results will be available to participants.

Protocol variations occurred during this trial due to the infection control procedures adopted during the COVID-19 pandemic. The statistical analysis will follow the guidelines for reporting completed trials modified due to the COVID-19 pandemic CONSERVE statement.[55]

Time frame
Recruitment commenced in mid-2017. Follow-up assessment is expected to conclude in 2023 when the final participant reaches 2 years corrected age.

Ethics and dissemination
The study will comply with the protocol, and the ethical principles of the Declaration of Helsinki, in accordance with the Guideline for Good Clinical Practice, and The National Statement on Ethical Conduct in Human Research (2007) updated in 2018. The study is approved by the Sydney Children's Hospital Network Ethics Committee in April 2017 (ref number HREC/17/SCHN/37) and the participating site institutions. On completion of the trial the study results will be published in an international peer-reviewed journal and disseminated via international conferences and patient websites in easy read format.

Data management
All participant information will be coded, with paper copies stored in a locked filing cabinet at Cerebral Palsy Alliance, and digital data on Cerebral Palsy Alliance password-protected database with 2-factor authentication, with the principal investigators the only people able to access the data. All measurable steps will be taken to ensure that health information collected is always protected. Any identification codes will be stored in a different secured password-protected place from the data

records to which they are linked. Additionally, all consent forms and identifiable information will be stored in a separate, locked filing cabinet to the research data. Data management will comply with relevant privacy protocols, including the Australian Standard on personal privacy protection.

Patient and public involvement
This study was codesigned and co-led by Shannon Olivey, a parent of a child with CP, who was an associate investigator. She contributed to the grant submission (ie, study design) and reviewed pertinent participant facing documents.

CONCLUSION
This trial has been designed to provide robust data on the efficacy of a novel early intervention (GAME, which uses goals, activities, and motor enrichment) designed to improve the motor skills of infants with CP. The results have the potential to produce significant and lasting motor and cognitive gains that lessen the severity of their CP and improve their quality of life, as well as reduce costs to parents and society.

Author affiliations
[1]Cerebral Palsy Alliance Research Institute, Discipline of Child and Adolescent Health, The University of Sydney, Sydney, New South Wales, Australia
[2]Grace Centre for Newborn Intensive Care, Sydney Children's Hospital Network, Sydney, New South Wales, Australia
[3]The Faculty of Medicine, Queensland Cerebral Palsy and Rehabilitation Research Centre, The University of Queensland, Brisbane, Queensland, Australia
[4]Faculty of Medicine, Dentistry and Health Sciences, University of Melbourne, Parkville, Victoria, Australia
[5]Children's Hospital at Westmead Clinical School, The University of Sydney, Sydney, New South Wales, Australia
[6]Faculty of Medicine and Health, NHMRC Clinical Trials Centre, The University of Sydney, Sydney, New South Wales, Australia
[7]Department of Paediatrics, Monash University, Clayton, Victoria, Australia
[8]Cerebral Palsy Alliance, Forestville, New South Wales, Australia
[9]Queensland Cerebral Palsy Research Centre, The University of Queensland, Brisbane, Queensland, Australia
[10]The Faculty of Medicine, Queensland Cerebral Palsy and Rehabilitation Research Centre, UQ Child Health Research Centre, The University of Queensland, Brisbane, Queensland, Australia
[11]Health and Biosecurity, The Australian E-Health Research Centre, CSIRO, Brisbane, Queensland, Australia
[12]NHMRC Clinical Trials Centre, University of Sydney, Sydney, New South Wales, Australia
[13]Faculty of Medicine and Health, The University of Sydney, Sydney, New South Wales, Australia
[14]RPA Newborn Care, Sydney Local Health District, Camperdown, New South Wales, Australia
[15]Medical Imaging Department, The Children's Hospital at Westmead, Sydney, New South Wales, Australia
[16]School of Allied Health, Curtin University, Perth, Western Australia, Australia
[17]Telethon Kids Institute, Nedlands, Western Australia, Australia
[18]Paediatric Rehabilitation, Princess Margaret Hospital for Children, Perth, Western Australia, Australia
[19]Department of Developmental Neuroscience, IRCCS Stella Maris, University of Pisa, Pisa, Toscana, Italy
[20]Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Toscana, Italy
[21]Faculty of Medicine & Health, The University of Sydney, Sydney, New South Wales, Australia

[22]Faculty of Medicine & Health, Cerebral Palsy Alliance Research Institute, Specialty of Child & Adolescent Health, Sydney Medical School, The University of Sydney, Sydney, New South Wales, Australia

ORCID iDs
Catherine Morgan http://orcid.org/0000-0003-3670-0845
Alicia J Spittle http://orcid.org/0000-0002-6535-661X
Koa Whittingham http://orcid.org/0000-0002-5344-9907

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