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Preschool HABIT-ILE: A randomised controlled trial to determine efficacy of intensive rehabilitation compared to usual care to improve motor skills of children, aged 2 to 5 years, with bilateral cerebral palsy.

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Abstract

Introduction: Young children with bilateral cerebral palsy (BCP) often experience difficulties with gross motor function, manual ability and posture, impacting developing independence in daily life activities, participation and quality of life. Hand Arm Bimanual Intensive Training Including Lower Extremity (HABIT-ILE) is a novel intensive motor intervention integrating upper and lower extremity training that has been developed and tested in older school-aged children with unilateral and BCP. This study aims to compare an adapted preschool version of HABIT-ILE to usual care in a randomised controlled trial.

Methods and analysis: 60 children with BCP aged 2-5 years, Gross Motor Function Classification System (GMFCS) II-IV will be recruited. Children will be stratified by GMFCS and randomised using concealed allocation to either receiving Preschool HABIT-ILE or usual care. Preschool HABIT-ILE will be delivered in groups of 4-6 children, for 4hrs/day for 10 days (total 40 hrs). Children receiving Preschool HABIT-ILE be provided a written home program with the aim of achieving an additional 10 hours of home practice (total dose 50 hours). Outcomes will be assessed at baseline, immediately following intervention and then retention of effects will be tested at 26 weeks. The primary outcome will be the Peabody Developmental Motors Scales–Second Edition to evaluate gross and fine motor skills. Secondary outcomes will be gross motor function, bimanual hand performance, self-care, mobility, goal attainment, global performance of daily activities, cognition and adaptive function, habitual physical activity and quality of life. Analyses will follow standard principles for RCTs using two-group comparisons on all participants on an intention-to-treat basis. Comparisons between groups for primary and secondary outcomes will be conducted using regression models.

Ethics and dissemination: Ethics approval has been granted by the Medical Research Ethics Committee Children's Health Queensland Hospital and Health Service Human Research Ethics Committee (HREC/19/QCHQ/59444) and The University of Queensland (2020000336/HREC/19/QCHQ/59444).

Trial registration number: Australian and New Zealand Clinical Trial Registry (ANZCTR: 12620000071921).

Keywords: cerebral palsy, children, gross motor function, manual ability, randomised controlled trial, hand arm bimanual intensive training including lower extremity, pre-school age.

Word count: 4998

Article Summary

Strengths and limitations of the study

- This randomised controlled trial investigates the efficacy of an intensive motor training approach to improve gross and fine motor skills, gross motor function and manual ability for young preschool aged children (2-5 years) with bilateral cerebral palsy, powered to test both primary and secondary outcomes.
- Potential participants will be recruited from one centre in Australia over a three year period, ensuring that the sample size of 60 children across GMFCS II-IV will be met.
- Outcomes include gross and fine motor skills, gross motor function, bimanual performance, self-care, mobility, perceived performance of and satisfaction with parent/caregiver defined occupational performance goals, cognition and adaptive function, habitual physical activity and quality of life.
- A fidelity framework includes standardised training of interventionists and fidelity monitoring of each intervention camp.
- A comprehensive within trial cost-utility analysis will be conducted to synthesize the costs and benefits of the Preschool HABIT-ILE program compared to usual care.
- Measures of neuroplasticity will not be performed as less feasible at this young age (requires sleeping scans after de-sensitization).

INTRODUCTION

In Australia, cerebral palsy (CP) is the most common physical disability in childhood with an estimated 35,000 people currently living with CP.[1] In high income countries, the birth prevalence of CP is falling, with Australia reporting a reduction from 1.9 to 1.4/1000 live births between 2007 and 2012.[1] In addition to the declining rate of CP, motor severity has also reduced, as has the frequency of comorbidities such as epilepsy and intellectual impairment.[1] The total cost of CP to the Australian economy is Aus$5.17 billion dollars, equivalent to AUS$145,662 per person with CP annually which includes both the financial costs, but also those associated with lost well-being.[2]

There is no cure for CP; it is a life-long condition characterized by increasing physical disability over time.[3] Over 61% of children with CP have bilateral motor involvement, where the motor disorder impacts both legs, trunk, and for some, one or both arms.[1] Interventions that reduce the impact of physical disability resulting from CP, and promote developing independence in daily life activities, inclusion and community participation are greatly needed. A recent systematic review of interventions for preventing and treating children with CP, suggested that given the reduction in both the prevalence and severity of CP (e.g. smaller brain injuries and greater baseline motor, sensory and learning ability), children may be more likely now than ever to respond positively to motor interventions.[4]

Contemporary proven motor interventions have largely targeted school-aged children with CP and focused on upper and lower extremity motor performance separately.[4 5] To date, significant evidence exists for intensive upper extremity interventions (≈60 hours) to enhance motor performance in children with unilateral CP.[5] A number of systematic reviews[4-6] have consistently identified growing evidence for intensive motor learning based approaches to upper limb rehabilitation for children with unilateral CP (e.g. constraint induced movement therapy, Hand Arm Bimanual Intensive Training [HABIT]) to improve upper limb motor performance. Interventions to target lower compared to upper limb motor performance have generally been less intensive. A recent systematic review identified mobility and treadmill training as effective green light, “do it” interventions to improve mobility and gait[4]. One model of intervention which integrates both upper and lower limb training was developed for

children with unilateral CP. Hand Arm Bimanual Intensive Training Including Lower Extremity training (HABIT-ILE)[7-9] is based on known principles of how to induce neuroplasticity incorporating specific, intensive, repetitive task practice. To date, two small trials of HABIT-ILE have been conducted, one with school aged children with unilateral CP (n=24)[8] and one for those with bilateral CP (n=20).[7] In children with bilateral CP, aged 6 to 15 years, there was a strong effect of HABIT-ILE to improve manual ability (1.6 logit increase on the ABILHAND-Kids), gross motor function (7 point increase on the Gross Motor Function Measure) and self-care (8 point increase on the Pediatric Evaluation of Disability Inventory Computer Adapted Test: PEDI-CAT).[7] A recent systematic review graded HABIT-ILE as a "yellow, probably do it" intervention, as results were promising, but require additional research to increase confidence in the estimate of treatment effect.[4] We are currently conducting a large clinical trial of HABIT-ILE for school aged children with bilateral CP to confirm and increase certainty in these results.[10]

To date, there remains a major gap in the current evidence for effective interventions for younger children (2-5yrs) with bilateral CP.[11] Children with CP reach 90% of their gross motor/movement potential by 5 years of age or younger, making the first 5 years of life a vital window of opportunity to maximize function.[12] In addition, this younger age group is less likely to have secondary complications such as muscle contractures, therefore the magnitude of outcomes possible could be larger than in older children. The current HABIT-ILE dosing schedule for school-aged children with bilateral CP (6.5 hrs/day for 10 days[10] or 6.5 hours for 13 days[7]) is not feasible to deliver to younger children. Content of therapy will differ as games will need to be carefully selected to be age appropriate to engage children and drive self-initiated mobility and bimanual hand use. An adapted dosing schedule and structure of HABIT-ILE needs to be urgently developed and evaluated for this younger age group, to capitalize on harnessing use-dependent neuroplasticity and maximising motor function.

This pragmatic randomised controlled trial (RCT), Preschool HABIT-ILE will compare this intensive motor training approach to usual care in preschool aged children with bilateral CP (2 to 5 years) at a lower dosing schedule (50 hours) than the original HABIT-ILE studies.[8 10] This lower dose was selected as it has been shown to be

acceptable, feasible and effective with a younger age group children[13] and will be augmented with a structured and written home program[14] to support families to carry out practice within their own context.

AIMS AND HYPOTHESES

Broad Aim

This RCT will be conducted in Queensland, Australia with 60 preschool aged children (2 to 5 years) with bilateral CP. This RCT with a pragmatic, single-blind design will determine if Preschool HABIT-ILE is more effective than usual care to improve gross and fine motor skills (Peabody Developmental Motor Scales – Second Edition: PDMS-2) immediately post intervention and retention at 26 weeks. Secondary outcomes will test the differential effects of Preschool HABIT-ILE compared to usual care on gross motor function (Gross Motor Function Measure 66: GMFM-66), bimanual performance (Both Hands Assessment: BoHA), self-care and mobility (PEDI-CAT), global performance of daily activities (ACTIVLIM-CP), performance of and satisfaction with parent/caregiver identified occupational performance goals (Canadian Occupational Performance Measure: COPM), executive functioning (Behavior Rating Inventory of Executive Function Preschool Version BRIEF-P), habitual physical activity (7-day free living accelerometry using ActiGraph GT3X+) and quality of life (Infant Toddler Quality of Life Questionnaire: ITQOL and the Child Health Utility Index: CHU9) immediately post intervention and retention at 26 weeks post intervention.

Primary Hypothesis

For preschool aged children with bilateral CP, Preschool HABIT-ILE for a duration of 50 hours, will be more effective than a control group receiving usual care to improve:

[i] gross and fine motor skills total score on the Peabody Developmental Motor Scales Second Edition (PDMS-2: difference of 7.5 Total Motor Quotient or equivalent to 0.5 standard deviation) at 3 weeks immediately post intervention with retention of treatment effects at 6 months post intervention.

Secondary Hypotheses

For preschool aged children with bilateral CP, Preschool HABIT-ILE for a duration of 50 hours will be more effective than a control group receiving usual care immediately post intervention and at 26 weeks post intervention to increase:

[ii] Gross motor function (GMFM-66)[15] motor capacity score;

[iii] Bimanual hand performance (BoHA)[16];

[iv] Self-care, mobility, social/cognitive and responsibilty (PEDI-CAT)[17];

[v] Performance and satisfaction scores on the COPM[18];

[vi] Global performance of daily activities (ACTIVLIM-CP)[19];

[vii] Executive functioning (BRIEF-P)[20];

[viii] Quality of Life (ITQOL; and the CHU9 parent proxy)[21 22];

[ix] Cost effectiveness $(\Delta\$Cost/\Delta CP\ QOL)$ of medical treatment received.

The following hypotheses relate to objective measurement of physical activity and upper limb movement using body-worn devices including optical heart rate sensors (Polar OH1) and body-worn accelerometers (ActiGraph GT3X+):

[x] Intensity of the camp, quantified by (1) estimated energy expenditure, (2) frequency and duration of detected activities, and (3) asymmetry index between upper limbs will decrease from day 1 to day 10 of camp;

[xi] Personalized activity classification machine learning models will have >80% sensitivity and specificity to detect/classify activity type and predict intensity of physical activities in a simulated free-living environment (camp) in preschool-aged children with bilateral CP[23];

[xii] Upper limb asymmetry index on the BoHA will decrease in children receiving Preschool HABIT-ILE as compared to control;

[xiii] Minutes/day of moderate to vigorous intensity physical activity and light intensity physical activity will increase, and minutes/day of sedentary behaviour will decrease in children receiving Preschool HABIT-ILE as compared to control;

[xiv] Children receiving Preschool HABIT-ILE as compared to control will demonstrate a greater proportion of total time in ambulatory, transition and standing activities (vs sitting and lying).

METHODS

Study Design

This study is a pragmatic RCT in 60 preschool aged children with bilateral CP, which aims to evaluate the effects of Preschool HABIT-ILE (4 hrs/day for 10 days + 10 hrs home practice =total 50 hrs) compared to usual care. The study design has been informed by CONSORT Guidelines[24] (see Figure 1).

Recruitment

Sixty preschool aged children between 2 years corrected age and 5 years 11 months of age at study entry with bilateral CP confirmed by a physician will be recruited. Families with a child meeting eligibility criteria will be invited to join the study through the Queensland Children's Hospital and the Queensland Cerebral Palsy and Rehabilitation Research Centre, The University of Queensland, Brisbane Australia. Recruitment will begin following ethical and governance approvals. Recruitment will draw upon current databases within each organization, and referrals from the clinical service. We do not anticipate problems with our plan to recruit 60 children with bilateral CP as 200 children in QLD are likely to be eligible (ACPR 2018). The investigators have a strong track record of successfully completing large clinical trials, with all studies achieving recruitment targets.[25-28]

Inclusion Criteria

To be eligible for inclusion, participants must be:

(a) diagnosed with bilateral CP (diplegia/triplegia/quadriplegia: all motor types), GMFCS II to IV;

(b) aged 2 to 5 years;

(c) able to grasp light objects and lift most impaired arm ≥15cm above a table surface;

(d) able to understand and follow instructions in order to complete testing.

Exclusion Criteria

(a) uncontrolled seizures in the previous 6 months (i.e. not controlled with medication as this would be a confound and/or exercise risk);

(b) Orthopaedic and/or neurological surgery in the 12 months prior to or scheduled during study period (eligible for inclusion if at least 12 months-post orthopedic and/or neurological surgery)

(c) a visual impairment interfering with treatment/testing; and

(d) unable to actively engage in the assessment process. This will be determined during screening/baseline assessment.

Randomisation

Children will be recruited in cohorts of 8-16 and stratified into 1 of 2 groups based on GMFCS (II vs. III-IV). After consent and baseline measures, children will be randomized to Preschool HABIT-ILE or control intervention through a computer-generated randomization sequence using the REDCap randomization module, determined by non-study personnel.

Blinding

All outcome assessments at each time point will be administered by experienced physiotherapists and occupational therapists. Objective measures of motor capacity (PDMS-2, BoHA, GMFM-66) will be videotaped and scored by trained raters blinded to group allocation and timing of assessments. Accelerometers will be mailed to participants to complete baseline physical activity monitoring prior to randomization. Questionnaire-based measures (ACTIVLIM-CP, ITQOL, CHU9D) will be entered directly into a secure, de-identified REDCap database or computer program (PEDI-CAT) by caregivers. Caregivers and therapists will be blinded to COPM Goal Performance and Satisfaction ratings from previous assessment timepoint/s. Following the baseline assessment and randomization, it will not be possible for participants and their caregivers to be blinded to group allocation.

Study Interventions

The Preschool HABIT-ILE and control interventions are summarised according to the Template for Intervention Description and Replication (TIDieR) Checklist[29] in Table 1.

Preschool HABIT-ILE is a motor learning approach that simultaneously addresses coordination of the upper and lower limbs.[9] Key elements of Preschool HABIT-ILE:

Dose: 40 hours of therapy achieved through a 2-week intensive group-delivered model for 4 hrs/day over 10 days (Monday to Friday) in addition to a home program for generalization of learning. Home program dose will aim to achieve a further 10 hours over the two week intervention period for a total dose of preschool HABIT-ILE of 50 hours.

Intensity: The level of intensity will be low to vigorous and will vary across the intervention session. Children will be wearing Polar OH1 Optical Heart Rate monitors during the intervention sessions which will be used in combination with accelerometry to assess intensity of physical activity.

Mode: Groups of 4-6 children (1:1 or 2:1 therapist: child ratio according to ability).

Content and tailoring: The intervention will be based on the child's motor abilities (determined at baseline), age, interests and caregiver-identified functional goals. Tasks/activities will be made incrementally more challenging. Practice will be embedded in play, using part and whole task practice with high repetition including (i) table top fine motor play-based activities; (ii) activities of daily living when sitting/standing/walking; and (iii) gross motor play. Lower extremity motor abilities and postural control will be progressed from lying to sitting on the floor and then to sitting on a small bench. Transitions will also be progressed from floor-to-sitting-to-standing.

Intervention providers: Physiotherapists and occupational therapists, who have completed standardized training and are experienced in delivering HABIT-ILE with older children will form the supervisory team overseeing delivery of Preschool HABIT-ILE. A speech pathologist will consult with the team if children have specific communication (receptive and/or expressive) or feeding difficulties. For 30 minutes, at the conclusion of each session, the child's treating therapy team will meet individually with the child's parent/caregiver/s (one-on one) and discuss the daily program and make suggestions about activities that could be practised at home. These will be detailed on a written Home Program and Practice Log completed by the caregiver. The Home Program activities will be reviewed daily by the child's treating therapy team in collaboration with the child's caregiver and updated as appropriate. Parents will be able to take short videos/photos of home practice activities on their smart phone if they wish to serve as a visual reminder for use at home. In addition, a Therapist Daily Activity Log will be completed by the therapy team. The Therapist Daily Activity Log is a daily record detailing each activity undertaken by the child. It includes the duration and type of activity (types), position (positions), and number of repetitions or successes (for timed tasks) to assess or monitor participant adherence to the intervention. Furthermore, in combination with videotape (detailed below), logs will act as ground-truth for sensor data in order to assess accuracy and validity of activity classification.

Location: Assessments will be conducted at the Centre for Children's Health Research and Queensland Children's Hospital. The intervention will be conducted at

the Queensland Paediatric Rehabilitation Service at the Queensland Children's Hospital, South Brisbane, Australia.

Usual Care: The control group will receive usual care over the six month control period which will vary from weekly to monthly therapy. We expect that the majority of children will be accessing usual care occupational therapy and physiotherapy at an average of one session per week, funded through the National Disability Insurance Scheme. Intervention approaches will be varied and may include neurodevelopmental therapy, developmental therapy, or motor learning-based approaches. Some children may receive alternative "intensive" models of therapy as part of usual care. Families of children in each group will keep a log of usual care therapy including, frequency, duration, mode and content.

Adverse events and safety

Any minor or major adverse event associated with Preschool HABIT-ILE will be screened on a daily basis by the treating therapist and will inform the Study Coordinator and Chief Investigators (except major adverse events or those requiring medical treatment, which must be reported as soon as possible, and within 24 hours). Minor adverse events include:

- Near miss accidents (such as falling off a tricycle or falling heavily in a game)
- Sore muscles, bruises, other minor injuries not requiring medical treatment
- Feeling upset, guilty, or sad or fatigued

Major adverse events include:

- Injuries that require medical treatment (such as moderate-severe strains or broken bones)

After reporting to the site Chief Investigator, local site processes will be followed as necessary.

Fidelity

Supervisory Team: Therapist Attributes

It is required that Preschool HABIT-ILE supervising therapists possess the following attributes:

- Full registration with the Australian Health Practitioner Regulation Agency (AHPRA, Physiotherapists and Occupational Therapists);
- Current Basic First Aid and Cardiac Pulmonary Resuscitation certificate;

- Evidence of immunization status (measles, mumps, rubella, pertussis, varicella, hepatitis B);
- Completed standardized training in HABIT-ILE and experience conducting a minimum of two HABIT-ILE camps with school aged children.

Intervention therapists/therapy students' attributes:

Delivery of the Preschool HABIT-ILE intervention will rely on volunteers including qualified physiotherapists (PT) and occupational therapists (OT) and undergraduate PT and OT therapy students. It is required that therapists/therapy students possess the following attributes:

- Full registration with the Australian Health Practitioner Regulation Agency (AHPRA, Physiotherapists and Occupational Therapists) OR evidence of enrolment in a relevant undergraduate course.
- Current Basic First Aid and Cardiac Pulmonary Resuscitation certificate;
- Evidence of immunization status.

Therapist/student Training

Standardized interventionist training developed by LS, SR, YB will be provided to therapists/students who will deliver the intervention. This will occur in the week prior to each camp. The one day training package will include:

- Intervention manual;
- Onsite training prior to Preschool HABIT-ILE camp led by the supervising team (LS, KM, MT, SR).

Training sessions will be video recorded and accessible at any time for established or new therapists delivering the intervention.

Fidelity monitoring

All group intervention sessions will be videotaped and a random selection viewed for fidelity adherence and competence criteria.

Screening and descriptive measures

All participants will be classified using the:

1. Mini-Manual Abilities Classification System (Mini-MACS): The Mini-MACS will classify the child's ability to hand objects in daily activities on a 5-level ordinal scale. The Mini-MACS was developed for children aged 1 to 4 years and has

excellent inter-rater reliability (ICC=0.97 between therapists; 0.90 between parents and therapists.[30]

2. Gross Motor Function Classification System Expanded and Revised (GMFCS): The GMFCS classifies the child's ability to carry out self-generated movements related to sitting and walking on a 5-level ordinal scale.[31] The GMFCS has established construct validity, and good inter-rater reliability between therapists.[32]
3. Communication Function Classification System (CFCS): The CFCS will be used to classify children's everyday performance of communicating using all methods (e.g. speech, gestures, eye gaze, augmentative and alternative communication) on a five-level ordinal scale.[33] There is evidence of content validity, good test re-test reliability, good interrater reliability (0.66) between professionals.[33 34]

Demographic Questionnaire: A study specific demographic questionnaire will collect information on the child's age, gender, co-morbidities, socio-economic status, family structure and supports, family income and current involvement in rehabilitation programs.

Previous medical history and assessments: Information and copies of Structural neuroimaging (sMRI at 1.5T or 3T) and history of early intervention (e.g. cooling, magnesium sulphate) will be retrieved from the child's medical records. Any sMRI will be retrieved and analysed using automated pipeline[35] and semi-quantitative scale of brain lesion severity.[36 37]

Primary outcomes

Fine and gross motor skills: The Peabody Developmental Motor Scales – Second Edition (PDMS-2)[38] will evaluate gross and fine motor skills. This standardised, norm reference measure for children from birth to 5 years of age, has been validated as a discriminative measure, and demonstrated responsiveness to change for toddlers with CP.[39]

Secondary outcomes

1. *Gross Motor Function:* Gross Motor Function Measure-66[15] (GMFM-66) is a criterion referenced observation measure developed using Rasch modelling to measure gross motor function of children with CP.[15]

2. *Bimanual Hand Performance:* Both Hands Assessment[16] (BoHA) measures how children with bilateral CP use their hands together in bimanual activities. Rasch measurement modelling showed strong evidence of internal construct validity, with two separate item difficulty hierarchies for children with: (a) symmetric upper limb use; (b) asymmetric upper limb use.[16] The test uses a selection of toys to elicit bimanual hand use in a structured play session. The BoHA takes 15 to 25 minutes to complete.
3. *Self-care, mobility, and social/cognitive functioning:* Pediatric Evaluation of Disability Inventory Computerised Assessment Test (PEDI-CAT): The PEDI-CAT[17] is a Rasch analysed parent completed questionnaire which measures ability in three functional domains of daily activities (self-care), mobility, and social/cognitive and one domain for responsibility (amount of assistance provided by caregivers to their child to complete complex daily tasks) using normative standard scores and scaled scores with good validity, reliability, and standardisation with typically developing children.[17 40] The "speedy" version will be used in order to minimise participant assessment burden.
4. *Performance and satisfaction with occupational performance goals:* The Canadian Occupational Performance Measure (COPM)[18] will be used to measure performance of and satisfaction with parent/caregiver defined self-care, leisure or productivity goals. Test retest reliability is high (ICC 0.76-0.89) and the COPM is responsive to change.[18] Parents/caregivers will set up to three occupational performance goals. Perceived performance of an individualized goal and satisfaction with performance is rated on a 1-10 scale with higher scores reflecting higher perceived performance and satisfaction.
5. *Global performance in daily activities:* The ACTIVLIM-CP is a Rasch analysed parent completed questionnaire covering a range of daily activities either involving the arms or legs, or both. The questionnaire comprises 43 items on a unidimensional scale, with high reliability (R=0.98) and reproducibility (R=0.97). The questionnaire is suitable for use with children aged 2 to 18 years.[19]
6. *Range of executive function:* Behavior Rating Inventory of Executive Function®—Preschool Version (BRIEF-P) measures multiple aspects of executive functioning; scales include Inhibit, Shift, Emotional Control, Working Memory, and Plan/Organize. BRIEF-P is useful in assessing preschool-aged children (aged 2 to 5 years 11 months) with acquired neurological, and developmental conditions.[20] A

single rating form allows parents to rate a child's executive functions within the context of his or her everyday environments. BRIEF-P Demonstrates high internal consistency reliability (0.80-0.95 for the parent sample and moderate test-retest reliability (0.78-0.90).[20]

7. *Objectively measured physical activity and upper limb movement:* The ActiGraph GT3X+ is a small (4.6cm x 3.3cm x 1.5cm) light weight (19g) triaxial accelerometer which provides valid assessments of habitual physical activity and bimanual performance in children with CP.[41 42] During the three assessment timepoints, one ActiGraph GT3X+ will be worn on each wrist, one additional ActiGraph GT3X+ will be worn on the less-affected thigh, and one Polar OH1 Optical HR Monitor will be worn on one upper arm during PDMS-2, BoHA, and GMFM-66 assessments. One week prior to each assessment time point, two ActiGraphs (1 less-affected thigh, 1 less-affected wrist) will also be worn in the participant's usual daily life at home (free living) for 7 days during all waking hours at each time-point to assess habitual physical activity. Throughout the 10 day HABIT-ILE intervention, children will wear one ActiGraph GT3X+ on each wrist and on the less-affected thigh, and one Polar OH1 Optical HR Monitor on one upper arm. Data will be processed using count-based methods to objectively quantify change in bimanual performance (asymmetry index) on the BoHA.[41] The intensity/type of practice during the camp, intensity of free-living habitual physical activity, and time spent ambulatory, transitioning and standing (vs sitting and lying) will be determined using machine learning approaches. HR and inertial data during assessments and camp will enable (1) testing of existing machine-learning models for activity classification,[23] (2) development of personalized machine-learning models which are hypothesized to be more accurate,[23] (3) quantification of the intensity and type of practice during the camp, (4) objective measurement of change in intensity and type of physical activity. Videotapes of therapy sessions and assessments will be used alongside the Therapist Daily Activity Logs as ground-truth for sensor data classification accuracy and validity analysis.
8. *Quality of life:* The Infant Toddler Quality of Life Questionnaire (ITQOL) is designed for infants aged 2 months to 5 years of age.[21] The ITQOL comprises 97 items, with good evidence for discriminative validity and reliability.[43] The Child Health Utility Index (CHU9)[22] is a paediatric health related quality of life measure

for use in economic evaluation. The measure consists of nine questions. In this study, the CHU9 will be completed by the child's primary caregiver.

Data Management

Data types:

We will collect objective data on fine and gross motor skills using the PDMS-2, gross motor function using the GMFM-66, bimanual hand performance using the BoHA, and objective physical activity and upper limb movement related to energy expenditure (Accelerometers and HR monitors). All measures are suitable for children 2 to 5 years of age with bilateral CP. Information collected from the child's primary caregiver includes: two questionnaire-based measures of self-care, mobility and global performance (PEDI-CAT, ACTIVLIM-CP), one questionnaire measuring cognition and adaptive function (BRIEF-P), three questionnaires assessing their child's quality of life (ITQOL, CHU9) and health resource use (HRU) which will be used for the health economic analysis. All data will be re-identifiable.

Data collection:

Data will be collected in one of four ways: (1) paper forms; (2) online survey platform (REDCap) instead of/in addition to paper forms; (3) devices (photo/video/audio recording devices and ActiGraph GT3X+, Polar OH1) ; or (4) face-to-face assessments with the child. All information will be coded with a participant ID number with any identification of codes (e.g. consent forms and other identifiable information) will be stored in a separate location. All data will be stored in electronic form on the Queensland Cerebral Palsy and Rehabilitation Research Centre, The University of Queensland secure server and REDCap (database) on secure Australian servers. Access to data will be limited to chief investigators and study coordinators as approved by the relevant ethics committees. Data management will comply with relevant privacy protocols, such as the Australian Standard on personal privacy protection.

Management of withdrawals

Participants can withdraw at any time with no penalty. Participants are informed of their right to withdraw at any time without consequences at the time of reading participant information forms and signing of consent forms. Participants that withdraw will not be replaced, as the a priori power calculation will account for a 20% dropout rate.

Sample Size Estimation

Based on a difference of 7.5 PDMS-2 Motor Quotients, with an alpha of 5% and 80% power, assuming a standard deviation of 9.2 and buffering for 20% attrition, a sample size of 60 will be required.[44] We will have 88% power to detect a difference of 5 points or greater on the GMFM-66 (assuming SD=6) and alpha=0.05.

Statistical Analysis

Analyses will follow standard principles for RCTs using two-group comparisons on all participants on an intention-to-treat basis. Primary comparison immediately post intervention (T2) based on PDMS-2 Total Motor Quotient scores will be between treatment groups using linear regression with treatment group (Preschool HABIT-ILE/control) included as the main effect and baseline PDMS-2 Motor Quotient as the covariable. Effect estimates will be presented as mean difference and 95% confidence interval. We will use similar methods to compare outcomes between groups immediately post intervention (T2) for gross motor function, bimanual hand function, self-care, mobility, global performance of daily activities, performance of and satisfaction with occupational performance goals, executive function and quality of life. In cases where interval data are not able to be transformed appropriately for regression analyses, non-parametric methods (Mann-Whitney U) will be used for between-treatment comparisons.

Health Economics

A within trial economic evaluation will be conducted to estimate the costs and outcomes of the Preschool HABIT-ILE therapy program. Resource utilization (staff time, equipment and facility use) associated with the delivery of the program will be collected alongside the RCT. Health care utilization will be assessed using a resource use questionnaire previously used in CP child and HABIT-ILE studies.[10 45] Utility will be derived from the CHU-9D[22], a generic child quality of life measure designed specifically for economic evaluation and which has been validated in an Australian population.[46] Incremental Cost Effectiveness Ratios (ICERs) will be estimated and where appropriate sensitivity analyses undertaken as in previous RCTs by our group.[47]

Ethics and dissemination

Full ethical approval has been granted by the Children's Health Queensland Hospital and Health Service Human Research Ethics Committee (HREC/19/QCHQ/59444), the Medical Research Ethics Committee of The University of Queensland (2020000336/HREC/19/QCHQ/59444). Participant information and consent forms

will be provided to all participants and their caregivers prior to entering the study. Full written and informed consent will be obtained from all caregivers of children participating in the trial. The trial has been registered with the Australian and New Zealand Clinical Trial Registry (ANZCTR: 12620000071921). This protocol is reported according to the Standard Protocol Items: Recommendations for Intervention Trials statement (SPIRIT)[48] and Template for Intervention Description and Replication Checklist (TIDieR).[29]

Findings will be disseminated via peer reviewed publication of study results, newsletter feedback to consumers and presentation at key national and international conferences. The authors will plan a knowledge translation pathway if the intervention proves effective in improving motor abilities of preschool aged children with bilateral CP.

Public/Patient Involvement Statement

Preschool HABIT-ILE was trialled in a truncated format in September 2019 (3 hours/day, 3 days/week for 1 week) with two participants (aged 3, GMFCS III and aged 5, GMFCS IV). Parents provided ongoing daily feedback on the feasibility and acceptability of Preschool HABIT-ILE, and confirmed our planned dosing schedule for the subsequent RCT. Participants and their families will be informed of progress and outcomes of this study via newsletter and conferences open to consumers.

DISCUSSION

Young children with CP reach 90% of their gross motor/movement potential by five years or younger.[12] Sixty percent of children with CP have a bilateral presentation of movement difficulties, yet there is limited evidence for effective interventions to improve their gross motor and manual abilities. Building on a previous small study[49] and our current HABIT-ILE Australia project[10], we aim to test the efficacy of an adapted protocol for younger children aged 2 to 5 years with bilateral CP to improve motor outcomes. One potential limitation of the study is that therapy students under the supervision of trained therapists will be primarily delivering the Preschool HABIT-ILE intervention. As we have done in the larger HABIT-ILE Australia study, we will account for this by providing one day of standardized training for all interventionists, daily debriefing meetings at the end of each day, and ongoing daily feedback from supervising therapists. Secondly, the dose being tested (50 hours) was a pragmatic choice based on what is likely to be feasible and acceptable in the Australian

context. This dose, however, relies on 10 hours of home practice. We will follow evidence-based processes for the development, delivery and support of parents and caregivers in the implementation of home practice.[14]

The study has a number of strengths. The number of participants to be included has been calculated for the primary clinical outcome and recruitment is feasible. Selected outcome measures have evidence for both validity and reliability in our population of interest. Standardized interventionist training and fidelity monitoring already developed in our HABIT-ILE Australia[10] study will be adapted, in addition to a with-in trial cost-utility analysis will provide vital information to inform the potential translation of this intervention, particularly in Australia under the National Disability Insurance Scheme. It is anticipated that results of this RCT will be disseminated widely through peer reviewed journals and academic conferences.

Figure 1. Participant flow diagram for Preschool HABIT-ILE.

Acknowledgments

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Competing Interests: None declared

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Author Contributions

LS is the chief investigator together with KM, YB and MT developed the intervention protocol. LS, RB, SR, MT and KM designed, established and achieved funding for this study. LS and SR are responsible for ethics applications and reporting. LS, KM, MT, AB, SR are responsible for recruitment and data collection. LS, SR, MT and KM are responsible for implementation of the interventionist training and fidelity monitoring. SR, ST, MA developed the protocol for evaluation of physical activity and upper limb movement. LS, KM, MT, SR, AB will take the lead roles on preparation for

publication of the clinical outcomes; DR, LS and RB will take lead roles of preparation of health economic publications. MC will provide biostatistical advice and oversight for all analyses and publications. LS and the CIs drafted the final version of this manuscript. All authors have contributed to the writing and critical review of the manuscript and have approved the final version. All data from this study will be submitted to peer review journals.

Table 1: TIDieR checklist[29] Comparison between Preschool HABIT-ILE and traditional "usual care" intervention

Item	Experimental Preschool HABIT-ILE	Control "usual care"
Name	Preschool Hand Arm Bimanual Intensive Training Including Lower Extremity	Traditional eclectic usual care
Why	Rationale: Intense, repetitive, active motor learning induces activity dependent neuroplasticity. Essential elements: a. Goal directed (goals defined by child/caregiver) b. Motor training with concurrent challenge for upper and lower limbs and posture c. Shaping d. Active practice of goals e. High repetition and intensity	Rationale: Usual care is highly variable, and may be based on biomechanical, neurodevelopmental, or motor learning principles. Elements may include: a. Goals defined by either caregiver OR therapist b. Stretching, splinting, casting c. Focus on developmental milestones d. Therapist physically facilitates more typical (normal) movement patterns with children who may be passive recipients e. May involve active goal practice using motor learning principles f. Equipment prescription
Materials	Therapy bench, fit ball to intensely and repeatedly challenge posture; developmentally appropriate	Splints, casts, adaptive equipment to compensate for tasks child cannot perform.

	activities/toys/games for children to actively develop bimanual hand skills with continuous practice of part and whole tasks through play. Whole task practice of individually identified functional goals with specific materials related to each goal.	
Who	Therapy students (physiotherapy, occupational therapy, exercise science), volunteer physiotherapists and occupational therapists working directly with child with a ratio of 2:1 interventionists/child. Experienced physiotherapists and occupational therapists who have completed standardised training in HABIT-ILE will supervise and mentor interventionists.	Occupational therapist and/or physiotherapist with the child and parents.
How	Clinic setting	Clinic, hospital, home or day care, preschool setting
How Much	4 hours/day for 10 weekdays over a 2 week period (total 40 hours) + home program for 10 hours over 2 weeks for a total dose of 50 hours	Weekly, monthly therapist provided ± home program. Highly variable. Some children may have access to other variations of intensive therapy interventions.
Tailoring	Tailored to the child's individually defined functional goals. Daily review of progress with a view to continually and incrementally increase the challenge	Highly variable.

How well	Daily video footage of participants at the day camp will be taken and reviewed by the supervising team every second to third day to ensure delivery of intervention as per protocol.	Detailed survey of parents about intervention approaches used.

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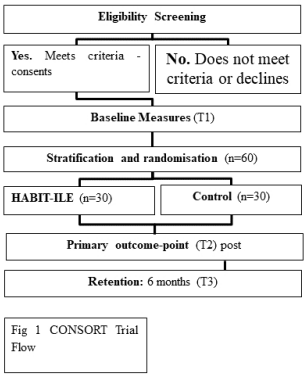

Fig 1 CONSORT Trial Flow

Figure 1. CONSORT Flow Chart

451x254mm (72 x 72 DPI)

Reporting checklist for protocol of a clinical trial.

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Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1

Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	
Protocol version	#3	Date and version identifier	footer
Funding	#4	Sources and types of financial, material, and other support	21
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1, 21-22
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	21-22
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and	21-22

		other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	6-7
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	6-7
Objectives	#7	Specific objectives or hypotheses	8
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	9-10
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	12

Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	10
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	11-12
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	18
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	13-14
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	13
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	15-17

Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Consort flow chart
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	18-19
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	10-11
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	10
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque,	10

		sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	10
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	10
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	-
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	14-17

Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	18
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	18
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	19
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	19
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	19
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and	NA

		competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	13
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	-
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	19
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	19-20

Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	19-20
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	11, 18
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	21
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	18
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	19-20

Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA

Appendices

Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	

BMJ Open

Preschool HABIT-ILE: Study protocol for a randomised controlled trial to determine efficacy of intensive rehabilitation compared to usual care to improve motor skills of children, aged 2 to 5 years, with bilateral cerebral palsy.

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Preschool HABIT-ILE: Study protocol for a randomised controlled trial to determine efficacy of intensive rehabilitation compared to usual care to improve motor skills of children, aged 2 to 5 years, with bilateral cerebral palsy.

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Abstract

Introduction: Young children with bilateral cerebral palsy (BCP) often experience difficulties with gross motor function, manual ability and posture, impacting developing independence in daily life activities, participation and quality of life. Hand Arm Bimanual Intensive Training Including Lower Extremity (HABIT-ILE) is a novel intensive motor intervention integrating upper and lower extremity training that has been developed and tested in older school-aged children with unilateral and BCP. This study aims to compare an adapted preschool version of HABIT-ILE to usual care in a randomised controlled trial.

Methods and analysis: 60 children with BCP aged 2-5 years, Gross Motor Function Classification System (GMFCS) II-IV will be recruited. Children will be stratified by GMFCS and randomised using concealed allocation to either receiving Preschool HABIT-ILE or usual care. Preschool HABIT-ILE will be delivered in groups of 4-6 children, for 4hrs/day for 10 days (total 40 hrs). Children receiving Preschool HABIT-ILE be provided a written home program with the aim of achieving an additional 10 hours of home practice (total dose 50 hours). Outcomes will be assessed at baseline, immediately following intervention and then retention of effects will be tested at 26 weeks. The primary outcome will be the Peabody Developmental Motors Scales–Second Edition to evaluate gross and fine motor skills. Secondary outcomes will be gross motor function (Gross Motor Function Measure-66), bimanual hand performance (Both Hands Assessment), self-care and mobility (Pediatric Evaluation of Disability Inventory-Computer Adapted Test), goal attainment (Canadian Occupational Performance Measure), global performance of daily activities (ACTIVLIM-CP), cognition and adaptive function (Behavior Rating Inventory of Executive Function®—Preschool Version), habitual physical activity (ActiGraph GT3X+) and quality of life (Infant Toddler Quality of Life Questionnaire and Child Health Utility Index-9). Analyses will follow standard principles for RCTs using two-group comparisons on all participants on an intention-to-treat basis. Comparisons between groups for primary and secondary outcomes will be conducted using regression models.

Ethics and dissemination: Ethics approval has been granted by the Medical Research Ethics Committee Children's Health Queensland Hospital and Health

Service Human Research Ethics Committee (HREC/19/QCHQ/59444) and The University of Queensland (2020000336/HREC/19/QCHQ/59444).

Trial registration number: Australian and New Zealand Clinical Trial Registry (ACTRN126200000719).

Keywords: gross motor function, manual ability, hand arm bimanual intensive training including lower extremity, pre-school age.

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Article Summary

Strengths and limitations of the study

- This randomised controlled trial investigates the efficacy of an intensive motor training approach to improve gross and fine motor skills, gross motor function and manual ability for young preschool aged children (2-5 years) with bilateral cerebral palsy, powered to test both primary and secondary outcomes.
- Potential participants will be recruited from one centre in Australia over a three year period, ensuring that the sample size of 60 children across GMFCS II-IV will be met.
- Outcomes include gross and fine motor skills, gross motor function, bimanual performance, self-care, mobility, perceived performance of and satisfaction with parent/caregiver defined occupational performance goals, cognition and adaptive function, habitual physical activity and quality of life.
- A fidelity framework includes standardised training of interventionists and fidelity monitoring of each intervention camp.
- A comprehensive within trial cost-utility analysis will be conducted to synthesize the costs and benefits of the Preschool HABIT-ILE program compared to usual care.

INTRODUCTION

In Australia, cerebral palsy (CP) is the most common physical disability in childhood with an estimated 35,000 people currently living with CP.[1] In high income countries, the birth prevalence of CP is falling, with Australia reporting a reduction from 1.9 to 1.4/1000 live births between 2007 and 2012.[1] In addition to the declining rate of CP, motor severity has also reduced, as has the frequency of comorbidities such as epilepsy and intellectual impairment.[1] The total cost of CP to the Australian economy is Aus$5.17 billion dollars, equivalent to AUS$145,662 per person with CP annually which includes both the financial costs, but also those associated with lost well-being.[2]

There is no cure for CP; it is a life-long condition characterized by increasing physical disability over time.[3] Over 61% of children with CP have bilateral motor involvement, where the motor disorder impacts both legs, trunk, and for some, one or both arms.[1] Interventions that reduce the impact of physical disability resulting from CP, and promote developing independence in daily life activities, inclusion and community participation are greatly needed. A recent systematic review of interventions for preventing and treating children with CP, suggested that given the reduction in both the prevalence and severity of CP (e.g. smaller brain injuries and greater baseline motor, sensory and learning ability), children may be more likely now than ever to respond positively to motor interventions.[4]

Contemporary proven motor interventions have largely targeted school-aged children with CP and focused on upper and lower extremity motor performance separately.[4 5] To date, significant evidence exists for intensive upper extremity interventions (≈60 hours) to enhance motor performance in children with unilateral CP.[5] A number of systematic reviews[4-6] have consistently identified growing evidence for intensive motor learning based approaches to upper limb rehabilitation for children with unilateral CP (e.g. constraint induced movement therapy, Hand Arm Bimanual Intensive Training [HABIT]) to improve upper limb motor performance. Interventions to target lower compared to upper limb motor performance have generally been less intensive. A recent systematic review identified mobility and treadmill training as effective green light, “do it” interventions to improve mobility and gait[4]. One model of intervention which integrates both upper and lower limb training was developed for

children with unilateral CP. Hand Arm Bimanual Intensive Training Including Lower Extremity training (HABIT-ILE)[7-9] is based on known principles of how to induce neuroplasticity incorporating specific, intensive, repetitive task practice. Studies in basic science with animal models, have demonstrated that early intervention based on motor learning principles at critical periods of development, reverse the secondary impact of inflammation post brain injury on neuroplastic processes such as axonal growth, synaptogenesis, myelination and neurogenesis[10-12]. To date, two small trials of HABIT-ILE have been conducted, one with school aged children with unilateral CP (n=24)[8] and one for those with bilateral CP (n=20).[7] In children with bilateral CP, aged 6 to 15 years, there was a strong effect of HABIT-ILE to improve manual ability (1.6 logit increase on the ABILHAND-Kids), gross motor function (7 point increase on the Gross Motor Function Measure) and self-care (8 point increase on the Pediatric Evaluation of Disability Inventory Computer Adapted Test: PEDI-CAT).[7] A recent systematic review graded HABIT-ILE as a "yellow, probably do it" intervention, as results were promising, but require additional research to increase confidence in the estimate of treatment effect.[4] We are currently conducting a large clinical trial of HABIT-ILE for school aged children with bilateral CP to confirm and increase certainty in these results.[13]

To date, there remains a major gap in the current evidence for effective interventions for younger children (2-5yrs) with bilateral CP.[14] Children with CP reach 90% of their gross motor/movement potential by 5 years of age or younger, making the first 5 years of life a vital window of opportunity to maximize function.[15] In addition, this younger age group is less likely to have secondary complications such as muscle contractures, therefore the magnitude of outcomes possible could be larger than in older children. The current HABIT-ILE dosing schedule for school-aged children with bilateral CP (6.5 hrs/day for 10 days[13] or 6.5 hours for 13 days[7]) is not feasible to deliver to younger children. Younger children often continue to require a nap time, and are unlikely able to tolerate 6.5 hrs per day of therapy without significant fatigue, therefore a reduced dosing protocol needs to be considered. Content of therapy will differ as games will need to be carefully selected to be age appropriate to engage children and drive self-initiated mobility and bimanual hand use. An adapted dosing schedule and structure of HABIT-ILE needs to be urgently developed and evaluated

for this younger age group, to capitalize on harnessing use-dependent neuroplasticity and maximising motor function.

This pragmatic randomised controlled trial (RCT), Preschool HABIT-ILE will compare this intensive motor training approach to usual care in preschool aged children with bilateral CP (2 to 5 years) at a lower dosing schedule (50 hours) than the original HABIT-ILE studies.[8 13] This lower dose was selected as it has been shown to be acceptable, feasible and effective with a younger age group children[16] and will be augmented with a structured and written home program[17] to support families to carry out practice within their own context.

AIMS AND HYPOTHESES

Broad Aim

This RCT will be conducted in Queensland, Australia with 60 preschool aged children (2 to 5 years) with bilateral CP. This RCT with a pragmatic, single-blind design will determine if Preschool HABIT-ILE is more effective than usual care to improve gross and fine motor skills (Peabody Developmental Motor Scales – Second Edition: PDMS-2) immediately post intervention and retention at 26 weeks. Secondary outcomes will test the differential effects of Preschool HABIT-ILE compared to usual care on gross motor function (Gross Motor Function Measure 66: GMFM-66), bimanual performance (Both Hands Assessment: BoHA), self-care and mobility (PEDI-CAT), global performance of daily activities (ACTIVLIM-CP), performance of and satisfaction with parent/caregiver identified occupational performance goals (Canadian Occupational Performance Measure: COPM), executive functioning (Behavior Rating Inventory of Executive Function Preschool Version BRIEF-P), habitual physical activity (7-day free living accelerometry using ActiGraph GT3X+) and quality of life (Infant Toddler Quality of Life Questionnaire: ITQOL and the Child Health Utility Index: CHU9) immediately post intervention and retention at 26 weeks post intervention.

Primary Hypothesis

For preschool aged children with bilateral CP, Preschool HABIT-ILE for a duration of 50 hours, will be more effective than usual care to improve:

[i] gross and fine motor skills total score on the Peabody Developmental Motor Scales Second Edition (PDMS-2: difference of 7.5 Total Motor Quotient or equivalent to 0.5 standard deviation) at 3 weeks post baseline (immediately post intervention) with retention of treatment effects at 6 months post intervention.

Secondary Hypotheses

For preschool aged children with bilateral CP, Preschool HABIT-ILE for a duration of 50 hours will be more effective than a control group receiving usual care immediately post intervention and at 26 weeks post intervention to increase:

[ii] Gross motor function (GMFM-66)[18] motor capacity score;

[iii] Bimanual hand performance (BoHA)[19];

[iv] Self-care, mobility, social/cognitive and responsibility (PEDI-CAT)[20];

[v] Performance and satisfaction scores on the COPM[21];

[vi] Global performance of daily activities (ACTIVLIM-CP)[22];

[vii] Executive functioning (BRIEF-P)[23];

[viii] Quality of Life (ITQOL; and the CHU9 parent proxy)[24 25];

[ix] Cost effectiveness $(\Delta\$Cost/\Delta CP\ QOL)$ of medical treatment received.

The following hypotheses relate to objective measurement of physical activity and upper limb movement using body-worn devices including optical heart rate sensors (Polar OH1) and body-worn accelerometers (ActiGraph GT3X+):

[x] Intensity of the camp, quantified by (1) estimated energy expenditure, (2) frequency and duration of detected activities, and (3) asymmetry index between upper limbs will decrease from day 1 to day 10 of camp;

[xi] Personalized activity classification machine learning models will have >80% sensitivity and specificity to detect/classify activity type and predict intensity of physical activities in a simulated free-living environment (camp) in preschool-aged children with bilateral CP[26];

[xii] Upper limb asymmetry index on the BoHA will decrease in children receiving Preschool HABIT-ILE as compared to control;

[xiii] Minutes/day of moderate to vigorous intensity physical activity and light intensity physical activity will increase, and minutes/day of sedentary behaviour will decrease in children receiving Preschool HABIT-ILE as compared to control;

[xiv] Children receiving Preschool HABIT-ILE as compared to control will demonstrate a greater proportion of total time in ambulatory, transition and standing activities (vs sitting and lying).

METHODS

Study Design

This study is a pragmatic RCT in 60 preschool aged children with bilateral CP, which aims to evaluate the effects of Preschool HABIT-ILE (4 hrs/day for 10 days + 10 hrs home practice =total 50 hrs) compared to usual care. The study design has been informed by CONSORT Guidelines[27] (see Figure 1).

Recruitment

Sixty preschool aged children between 2 years corrected age and 5 years 11 months of age at study entry with bilateral CP confirmed by a physician will be recruited. Families with a child meeting eligibility criteria will be invited to join the study through the Queensland Children's Hospital and the Queensland Cerebral Palsy and Rehabilitation Research Centre, The University of Queensland, Brisbane Australia. Recruitment will begin following ethical and governance approvals. Recruitment will draw upon current databases within each organization, and referrals from the clinical service. We do not anticipate problems with our plan to recruit 60 children with bilateral CP as 200 children in QLD are likely to be eligible (ACPR 2018). The investigators have a strong track record of successfully completing large clinical trials, with all studies achieving recruitment targets.[28-31]

Inclusion Criteria

To be eligible for inclusion, participants must be:

(a) diagnosed with bilateral CP (diplegia/triplegia/quadriplegia: all motor types), and classified in GMFCS levels II to IV and Manual Abilities Classification System (MACS) / mini-MACS levels I-III;

(b) aged 2 to 5 years;

(c) able to grasp light objects and lift most impaired arm ≥15cm above a table surface;

(d) able to understand and follow instructions in order to complete testing and intervention.

Exclusion Criteria

(a) uncontrolled seizures in the previous 6 months (i.e. not controlled with medication as this would be a confound and/or exercise risk);
(b) Orthopaedic and/or neurological surgery in the 12 months prior to or scheduled during study period (eligible for inclusion if at least 12 months-post orthopedic and/or neurological surgery)
(c) a visual impairment interfering with treatment/testing; and
(d) unable to actively engage in the assessment process. This will be determined during screening/baseline assessment.

Randomisation

Children will be recruited in cohorts of 8-12 and stratified into 1 of 2 groups based on GMFCS (II vs. III-IV). After consent and baseline measures, children will be randomized to Preschool HABIT-ILE or control intervention through a computer-generated randomization sequence using the REDCap randomization module, determined by non-study personnel.

Blinding

All outcome assessments at each time point will be administered by experienced physiotherapists and occupational therapists. Objective measures of motor capacity (PDMS-2, BoHA, GMFM-66) will be videotaped and scored by trained raters blinded to group allocation and timing of assessments. Accelerometers will be mailed to participants to complete baseline physical activity monitoring prior to randomization. Questionnaire-based measures (ACTIVLIM-CP, ITQOL, CHU9D) will be entered directly into a secure, de-identified REDCap database or computer program (PEDI-CAT) by caregivers. Caregivers and therapists will be blinded to COPM Goal Performance and Satisfaction ratings from previous assessment timepoint/s. Following the baseline assessment and randomization, it will not be possible for participants and their caregivers to be blinded to group allocation.

Study Interventions

The Preschool HABIT-ILE and control interventions are summarised according to the Template for Intervention Description and Replication (TIDieR) Checklist[32] in Table 1.

Preschool HABIT-ILE is a motor learning approach that simultaneously addresses coordination of the upper and lower limbs.[9] Key elements of Preschool HABIT-ILE:

Dose: 40 hours of therapy achieved through a 2-week intensive group-delivered model for 4 hrs/day over 10 days (Monday to Friday) in addition to a home program for generalization of learning. Home program dose will aim to achieve a further 10 hours over the two week intervention period for a total dose of preschool HABIT-ILE of 50 hours.

Intensity: The level of intensity will be low to vigorous and will vary across the intervention session. Children will be wearing Polar OH1 Optical Heart Rate monitors during the intervention sessions which will be used in combination with accelerometry to assess intensity of physical activity.

Mode: Groups of 4-6 children (1:1 or 2:1 therapist: child ratio according to ability).

Content and tailoring: The intervention will be based on the child's motor abilities (determined at baseline), age, interests and caregiver-identified functional goals. Tasks/activities will be made incrementally more challenging. Practice will be embedded in play, using part and whole task practice with high repetition including (i) table top fine motor play-based activities; (ii) activities of daily living when sitting/standing/walking; and (iii) gross motor play. Lower extremity motor abilities and postural control will be progressed from lying to sitting on the floor and then to sitting on a small bench. Transitions will also be progressed from floor-to-sitting-to-standing.

Intervention providers: Physiotherapists and occupational therapists, who have completed standardized training and are experienced in delivering HABIT-ILE with older children will form the supervisory team overseeing delivery of Preschool HABIT-ILE. A speech pathologist will consult with the team if children have specific communication (receptive and/or expressive) or feeding difficulties. For 30 minutes, at the conclusion of each session, the child's treating therapy team will meet individually with the child's parent/caregiver/s (one-on one) and discuss the daily program and make suggestions about activities that could be practised at home. These will be detailed on a written Home Program and Practice Log completed by the caregiver. The Home Program activities will be reviewed daily by the child's treating therapy team in collaboration with the child's caregiver and updated as appropriate. Parents will be able to take short videos/photos of home practice activities on their smart phone if they wish to serve as a visual reminder for use at home. In addition, a Therapist Daily Activity Log will be completed by the therapy

team. The Therapist Daily Activity Log is a daily record detailing each activity undertaken by the child. It includes the duration and type of activity (types), position (positions), and number of repetitions or successes (for timed tasks) to assess or monitor participant adherence to the intervention. Furthermore, in combination with videotape (detailed below), logs will act as ground-truth for sensor data in order to assess accuracy and validity of activity classification.

Location: Assessments will be conducted at the Centre for Children's Health Research and Queensland Children's Hospital. The intervention will be conducted at the Queensland Paediatric Rehabilitation Service at the Queensland Children's Hospital, South Brisbane, Australia.

Following completion of the HABIT-ILE program, children will return to their usual care therapies.

Usual Care: The control group will receive usual care over the six month control period which will vary from weekly to monthly therapy. We expect that the majority of children will be accessing usual care occupational therapy and physiotherapy at an average of one session per week, funded through the National Disability Insurance Scheme. Intervention approaches will be varied and may include neurodevelopmental therapy, developmental therapy, or motor learning-based approaches. Some children may receive alternative "intensive" models of therapy as part of usual care. Families of children in each group will keep a log of usual care therapy including, frequency, duration, mode and content.

Adverse events and safety

Any minor or major adverse event associated with Preschool HABIT-ILE will be screened on a daily basis by the treating therapist and will inform the Study Coordinator and Chief Investigators (except major adverse events or those requiring medical treatment, which must be reported as soon as possible, and within 24 hours). Minor adverse events include:

- Near miss accidents (such as falling off a tricycle or falling heavily in a game)
- Sore muscles, bruises, other minor injuries not requiring medical treatment
- Feeling upset, guilty, or sad or fatigued

Major adverse events include:

- Injuries that require medical treatment (such as moderate-severe strains or broken bones)

After reporting to the site Chief Investigator, local site processes will be followed as necessary.

Fidelity

Supervisory Team: Therapist Attributes

It is required that Preschool HABIT-ILE supervising therapists possess the following attributes:

- Full registration with the Australian Health Practitioner Regulation Agency (AHPRA, Physiotherapists and Occupational Therapists);
- Current Basic First Aid and Cardiac Pulmonary Resuscitation certificate;
- Evidence of immunization status (measles, mumps, rubella, pertussis, varicella, hepatitis B);
- Completed standardized training in HABIT-ILE and experience conducting a minimum of two HABIT-ILE camps with school aged children.

Intervention therapists/therapy students' attributes:

Delivery of the Preschool HABIT-ILE intervention will rely on volunteers including qualified physiotherapists (PT) and occupational therapists (OT) and undergraduate PT and OT therapy students. It is required that therapists/therapy students possess the following attributes:

- Full registration with the Australian Health Practitioner Regulation Agency (AHPRA, Physiotherapists and Occupational Therapists) OR evidence of enrolment in a relevant undergraduate course.
- Current Basic First Aid and Cardiac Pulmonary Resuscitation certificate;
- Evidence of immunization status.

Therapist/student Training

Standardized interventionist training developed by LS, SR, YB will be provided to therapists/students who will deliver the intervention. This will occur in the week prior to each camp. The one day training package will include:

- Intervention manual;
- Onsite training prior to Preschool HABIT-ILE camp led by the supervising team (LS, KM, MT, SR).

Training sessions will be video recorded and accessible at any time for established or new therapists delivering the intervention.

Fidelity monitoring

All group intervention sessions will be videotaped and a random selection viewed for fidelity adherence and competence criteria.

Screening and descriptive measures

All participants will be classified using the:

1. Mini-Manual Abilities Classification System (Mini-MACS): The Mini-MACS will classify the child's ability to hand objects in daily activities on a 5-level ordinal scale. The Mini-MACS was developed for children aged 1 to 4 years and has excellent inter-rater reliability (ICC=0.97 between therapists; 0.90 between parents and therapists.[33] The MACS will be used for children over 4 years of age.[34]
2. Gross Motor Function Classification System Expanded and Revised (GMFCS): The GMFCS classifies the child's ability to carry out self-generated movements related to sitting and walking on a 5-level ordinal scale.[35] The GMFCS has established construct validity, and good inter-rater reliability between therapists.[36]
3. Communication Function Classification System (CFCS): The CFCS will be used to classify children's everyday performance of communicating using all methods (e.g. speech, gestures, eye gaze, augmentative and alternative communication) on a five-level ordinal scale.[37] There is evidence of content validity, good test re-test reliability, good interrater reliability (0.66) between professionals.[37 38]

Two qualified, experienced occupational therapists and/or physiotherapists will perform classification at the baseline appointment and will achieve consensus by discussion.

Demographic Questionnaire: A study specific demographic questionnaire will collect information on the child's age, gender, co-morbidities, socio-economic status, family structure and supports, family income and current involvement in rehabilitation programs.

Previous medical history and assessments: Information and copies of Structural neuroimaging (sMRI at 1.5T or 3T) and history of early intervention (e.g. cooling, magnesium sulphate) will be retrieved from the child's medical records. Any sMRI will be retrieved and analysed using automated pipeline[39] and semi-quantitative scale of brain lesion severity.[40 41]

Primary outcomes

Fine and gross motor skills: The Peabody Developmental Motor Scales – Second Edition (PDMS-2)[42] will evaluate gross and fine motor skills. This standardised, norm reference measure for children from birth to 5 years of age, has been validated as a discriminative measure, and demonstrated responsiveness to change for toddlers with CP.[43]

Secondary outcomes

1. *Gross Motor Function:* Gross Motor Function Measure-66[18] (GMFM-66) is a criterion referenced observation measure developed using Rasch modelling to measure gross motor function of children with CP.[18]
2. *Bimanual Hand Performance:* Both Hands Assessment[19] (BoHA) measures how children with bilateral CP use their hands together in bimanual activities. Rasch measurement modelling showed strong evidence of internal construct validity, with two separate item difficulty hierarchies for children with: (a) symmetric upper limb use; (b) asymmetric upper limb use.[19] The test uses a selection of toys to elicit bimanual hand use in a structured play session. The BoHA takes 15 to 25 minutes to complete. The BoHA is the only available observational measure of bimanual performance validated for children with bilateral CP, MACS Levels I-III.
3. *Self-care, mobility, and social/cognitive functioning:* Pediatric Evaluation of Disability Inventory Computerised Assessment Test (PEDI-CAT): The PEDI-CAT[20] is a Rasch analysed parent completed questionnaire which measures ability in three functional domains of daily activities (self-care), mobility, and social/cognitive and one domain for responsibility (amount of assistance provided by caregivers to their child to complete complex daily tasks) using normative standard scores and scaled scores with good validity, reliability, and standardisation with typically developing children.[20 44] The "speedy" version will be used in order to minimise participant assessment burden.

4. *Performance and satisfaction with occupational performance goals:* The Canadian Occupational Performance Measure (COPM)[21] will be used to measure performance of and satisfaction with parent/caregiver defined self-care, leisure or productivity goals. Test retest reliability is high (ICC 0.76-0.89) and the COPM is responsive to change.[21] Parents/caregivers will set up to three occupational performance goals. Perceived performance of an individualized goal and satisfaction with performance is rated on a 1-10 scale with higher scores reflecting higher perceived performance and satisfaction.
5. *Global performance in daily activities:* The ACTIVLIM-CP is a Rasch analysed parent completed questionnaire covering a range of daily activities either involving the arms or legs, or both. The questionnaire comprises 43 items on a unidimensional scale, with high reliability (R=0.98) and reproducibility (R=0.97). The questionnaire is suitable for use with children aged 2 to 18 years.[22]
6. *Range of executive function:* Behavior Rating Inventory of Executive Function®—Preschool Version (BRIEF-P) measures multiple aspects of executive functioning; scales include Inhibit, Shift, Emotional Control, Working Memory, and Plan/Organize. BRIEF-P is useful in assessing preschool-aged children (aged 2 to 5 years 11 months) with acquired neurological, and developmental conditions.[23] A single rating form allows parents to rate a child's executive functions within the context of his or her everyday environments. BRIEF-P Demonstrates high internal consistency reliability (0.80-0.95 for the parent sample and moderate test-retest reliability (0.78-0.90).[23]
7. *Objectively measured physical activity and upper limb movement:* The ActiGraph GT3X+ is a small (4.6cm x 3.3cm x 1.5cm) light weight (19g) triaxial accelerometer which provides valid assessments of habitual physical activity and bimanual performance in children with CP.[45 46] During the three assessment timepoints, one ActiGraph GT3X+ will be worn on each wrist, one additional ActiGraph GT3X+ will be worn on the less-affected thigh, and one Polar OH1 Optical HR Monitor will be worn on one upper arm during PDMS-2, BoHA, and GMFM-66 assessments. One week prior to each assessment time point, two ActiGraphs (1 less-affected thigh, 1 less-affected wrist) will also be worn in the participant's usual daily life at home (free living) for 7 days during all waking hours at each time-point to assess habitual physical activity. During this time, parents will complete a log book to record their child's activity and position throughout

each day. Throughout the 10 day HABIT-ILE intervention, children will wear one ActiGraph GT3X+ on each wrist and on the less-affected thigh, and one Polar OH1 Optical HR Monitor on one upper arm. Data will be processed using count-based methods to objectively quantify change in bimanual performance (asymmetry index) on the BoHA.[45] The intensity/type of practice during the camp, intensity of free-living habitual physical activity, and time spent ambulatory, transitioning and standing (vs sitting and lying) will be determined using machine learning approaches. HR and inertial data during assessments and camp will enable (1) testing of existing machine-learning models for activity classification,[26] (2) development of personalized machine-learning models which are hypothesized to be more accurate,[26] (3) quantification of the intensity and type of practice during the camp, (4) objective measurement of change in intensity and type of physical activity. Videotapes of therapy sessions and assessments will be used alongside the Therapist Daily Activity Logs as ground-truth for sensor data classification accuracy and validity analysis.

8. *Quality of life:* The Infant Toddler Quality of Life Questionnaire (ITQOL) is designed for infants aged 2 months to 5 years of age.[24] The ITQOL comprises 97 items, with good evidence for discriminative validity and reliability.[47] The Child Health Utility Index (CHU9)[25] is a paediatric health related quality of life measure for use in economic evaluation along with a specifically design Health Resource Use (HRU) questionnaire. The measure consists of nine questions. In this study, the CHU9 will be completed by the child's primary caregiver.

Data Management

Data types:

We will collect objective data on fine and gross motor skills using the PDMS-2, gross motor function using the GMFM-66, bimanual hand performance using the BoHA, and objective physical activity and upper limb movement related to energy expenditure (Accelerometers and HR monitors). All measures are suitable for children 2 to 5 years of age with bilateral CP. Information collected from the child's primary caregiver includes: two questionnaire-based measures of self-care, mobility and global performance (PEDI-CAT, ACTIVLIM-CP), one questionnaire measuring cognition and adaptive function (BRIEF-P), three questionnaires assessing their child's quality of life (ITQOL, CHU9) and health resource use (HRU) which will be used for the health economic analysis. All data will be re-identifiable.

Data collection:

Data will be collected in one of four ways: (1) paper forms; (2) online survey platform (REDCap) instead of/in addition to paper forms; (3) devices (photo/video/audio recording devices and ActiGraph GT3X+, Polar OH1) ; or (4) face-to-face assessments with the child. All information will be coded with a participant ID number with any identification of codes (e.g. consent forms and other identifiable information) will be stored in a separate location. All data will be stored in electronic form on the Queensland Cerebral Palsy and Rehabilitation Research Centre, The University of Queensland secure server and REDCap (database) on secure Australian servers. Access to data will be limited to chief investigators and study coordinators as approved by the relevant ethics committees. Data management will comply with relevant privacy protocols, such as the Australian Standard on personal privacy protection.

Management of withdrawals

Participants can withdraw at any time with no penalty. Participants are informed of their right to withdraw at any time without consequences at the time of reading participant information forms and signing of consent forms. Participants that withdraw will not be replaced, as the a priori power calculation will account for a 20% dropout rate.

Sample Size Estimation

Based on a difference of 7.5 PDMS-2 Motor Quotients, with an alpha of 5% and 80% power, assuming a standard deviation of 9.2 and buffering for 20% attrition, a sample size of 60 will be required.[48] We will have 88% power to detect a difference of 5 points or greater on the GMFM-66 (assuming SD=6) and alpha=0.05.

Statistical Analysis

Analyses will follow standard principles for RCTs using two-group comparisons on all participants on an intention-to-treat basis. Primary comparison immediately post intervention (T2) based on PDMS-2 Total Motor Quotient scores will be between treatment groups using linear regression with treatment group (Preschool HABIT-ILE/control) included as the main effect and baseline PDMS-2 Motor Quotient as the covariable. Effect estimates will be presented as mean difference and 95% confidence interval. We will use similar methods to compare outcomes between groups immediately post intervention (T2) and at 6 months post intervention (T3) for gross motor function, bimanual hand function, self-care, mobility, global performance

of daily activities, performance of and satisfaction with occupational performance goals, executive function and quality of life. In cases where interval data are not able to be transformed appropriately for regression analyses, non-parametric methods (Mann-Whitney U) will be used for between-treatment comparisons.

Health Economics

A within trial economic evaluation will be conducted to estimate the costs and outcomes of the Preschool HABIT-ILE therapy program. Resource utilization (staff time, equipment and facility use) associated with the delivery of the program will be collected alongside the RCT. Health care utilization will be assessed using a resource use questionnaire previously used in CP child and HABIT-ILE studies.[13 49] Utility will be derived from the CHU-9D[25], a generic child quality of life measure designed specifically for economic evaluation and which has been validated in an Australian population.[50] Incremental Cost Effectiveness Ratios (ICERs) will be estimated and where appropriate sensitivity analyses undertaken as in previous RCTs by our group.[51]

Ethics and dissemination

Full ethical approval has been granted by the Children's Health Queensland Hospital and Health Service Human Research Ethics Committee (HREC/19/QCHQ/59444), the Medical Research Ethics Committee of The University of Queensland (2020000336/HREC/19/QCHQ/59444). Participant information and consent forms will be provided to all participants and their caregivers prior to entering the study. Full written and informed consent will be obtained from all caregivers of children participating in the trial. The trial has been registered with the Australian and New Zealand Clinical Trial Registry (ACTRN126200000719p). This protocol is reported according to the Standard Protocol Items: Recommendations for Intervention Trials statement (SPIRIT)[52] and Template for Intervention Description and Replication Checklist (TIDieR).[32]

Findings will be disseminated via peer reviewed publication of study results, newsletter feedback to consumers and presentation at key national and international conferences. The authors will plan a knowledge translation pathway if the intervention proves effective in improving motor abilities of preschool aged children with bilateral CP.

Public/Patient Involvement Statement

Preschool HABIT-ILE was trialled in a truncated format in September 2019 (3 hours/day, 3 days/week for 1 week) with two participants (aged 3, GMFCS III and aged 5, GMFCS IV). Parents provided ongoing daily feedback on the feasibility and acceptability of Preschool HABIT-ILE, and confirmed our planned dosing schedule for the subsequent RCT. Participants and their families will be informed of progress and outcomes of this study via newsletter and conferences open to consumers.

DISCUSSION

Young children with CP reach 90% of their gross motor/movement potential by five years or younger.[15] Sixty percent of children with CP have a bilateral presentation of movement difficulties, yet there is limited evidence for effective interventions to improve their gross motor and manual abilities[53]. Building on a previous small study[49] and our current HABIT-ILE Australia project[13], we aim to test the efficacy of an adapted protocol for younger children aged 2 to 5 years with bilateral CP to improve motor outcomes. One potential limitation of the study is that therapy students under the supervision of trained therapists will be primarily delivering the Preschool HABIT-ILE intervention. As we have done in the larger HABIT-ILE Australia study, we will account for this by providing one day of standardized training for all interventionists, daily debriefing meetings at the end of each day, and ongoing daily feedback from supervising therapists. Secondly, the dose being tested (50 hours) was a pragmatic choice based on what is likely to be feasible and acceptable in the Australian context. This dose, however, relies on 10 hours of home practice. We will follow evidence-based processes for the development, delivery and support of parents and caregivers in the implementation of home practice.[17] Usual care is highly variable and may not be at an equivalent dose as the intended Preschool HABIT-ILE. It is not possible to standardize usual care given it is delivered by many different service providers under pre-agreed funding packages. We will however, comprehensively record the type and dose of standard care to determine any differences in dosing schedules and content of intervention. Our inclusion of children classified GMFCS II to IV with all motor types aims to ensure that results are generalizable, however if there is a large differential response to the intervention, the study may be underpowered.

The study has a number of strengths. The number of participants to be included has been calculated for the primary clinical outcome and recruitment is feasible. Selected outcome measures have evidence for both validity and reliability in our population of interest. Standardized interventionist training and fidelity monitoring already developed in our HABIT-ILE Australia[10] study will be adapted, in addition to a with-in trial cost-utility analysis will provide vital information to inform the potential translation of this intervention, particularly in Australia under the National Disability Insurance Scheme. It is anticipated that results of this RCT will be disseminated widely through peer reviewed journals and academic conferences.

Figure 1. Participant flow diagram for Preschool HABIT-ILE.

Trial Status Update

The study was temporarily paused due to COVID-19. Recruitment has commenced in October 2020 and anticipated commencement of the intervention is in March 2021. A 12 month no cost extension on the grant funding this project has been provided.

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Competing Interests: None declared

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Author Contributions

LS is the chief investigator together with KM, YB and MT developed the intervention protocol. LS, RB, SR, MT and KM designed, established and achieved funding for this study. LS and SR are responsible for ethics applications and reporting. LS, KM, MT, AB, SR are responsible for recruitment and data collection. LS, SR, MT and KM

are responsible for implementation of the interventionist training and fidelity monitoring. SR, ST, MA developed the protocol for evaluation of physical activity and upper limb movement. LS, KM, MT, SR, AB will take the lead roles on preparation for publication of the clinical outcomes; DR, LS and RB will take lead roles of preparation of health economic publications. MC will provide biostatistical advice and oversight for all analyses and publications. LS and the chief investigators drafted the final version of this manuscript. All authors have contributed to the writing and critical review of the manuscript and have approved the final version. All data from this study will be submitted to peer review journals.

Table 1: TIDieR checklist[32] Comparison between Preschool HABIT-ILE and traditional "usual care" intervention

Item	Experimental Preschool HABIT-ILE	Control "usual care"
Name	Preschool Hand Arm Bimanual Intensive Training Including Lower Extremity	Traditional eclectic usual care
Why	Rationale: Intense, repetitive, active motor learning induces activity dependent neuroplasticity. Essential elements: a. Goal directed (goals defined by child/caregiver) b. Motor training with concurrent challenge for upper and lower limbs and posture c. Shaping d. Active practice of goals e. High repetition and intensity	Rationale: Usual care is highly variable, and may be based on biomechanical, neurodevelopmental, or motor learning principles. Elements may include: a. Goals defined by either caregiver OR therapist b. Stretching, splinting, casting c. Focus on developmental milestones d. Therapist physically facilitates more typical (normal) movement patterns with children who may be passive recipients e. May involve active goal practice using motor learning principles f. Equipment prescription
Materials	Therapy bench, fit ball to intensely and repeatedly challenge posture; developmentally appropriate	Splints, casts, adaptive equipment to compensate for tasks child cannot perform.

	activities/toys/games for children to actively develop bimanual hand skills with continuous practice of part and whole tasks through play. Whole task practice of individually identified functional goals with specific materials related to each goal.	
Who	Therapy students (physiotherapy, occupational therapy, exercise science), volunteer physiotherapists and occupational therapists working directly with child with a ratio of 2:1 interventionists/child. Experienced physiotherapists and occupational therapists who have completed standardised training in HABIT-ILE will supervise and mentor interventionists.	Occupational therapist and/or physiotherapist with the child and parents.
How	Clinic setting	Clinic, hospital, home or day care, preschool setting
How Much	4 hours/day for 10 weekdays over a 2 week period (total 40 hours) + home program for 10 hours over 2 weeks for a total dose of 50 hours	Weekly, monthly therapist provided ± home program. Highly variable. Some children may have access to other variations of intensive therapy interventions.
Tailoring	Tailored to the child's individually defined functional goals. Daily review of progress with a view to continually and incrementally increase the challenge	Highly variable.

How well	Daily video footage of participants at the day camp will be taken and reviewed by the supervising team every second to third day to ensure delivery of intervention as per protocol.	Detailed survey of parents about intervention approaches used.

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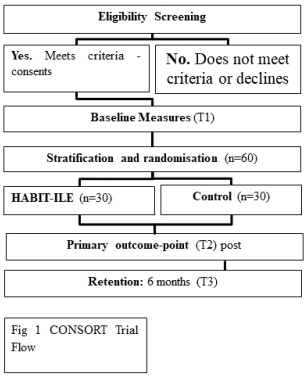

Figure 1. CONSORT Flow Chart

451x254mm (72 x 72 DPI)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1

Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	
Protocol version	#3	Date and version identifier	footer
Funding	#4	Sources and types of financial, material, and other support	21
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1, 21-22
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	21-22
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and	21-22

		other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	6-7
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	6-7
Objectives	#7	Specific objectives or hypotheses	8
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	9-10
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	12

Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	10
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	11-12
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	18
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	13-14
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	13
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	15-17

Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Consort flow chart
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	18-19
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	10-11
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	10
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque,	10

		sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	10
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	10
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	-
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	14-17

Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	18
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	18
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	19
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	19
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	19
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and	NA

		competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	13
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	-
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	19
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	19-20

Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	19-20
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	11, 18
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	21
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	18
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	19-20

Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	

BMJ Open

Preschool HABIT-ILE: Study protocol for a randomised controlled trial to determine efficacy of intensive rehabilitation compared to usual care to improve motor skills of children, aged 2 to 5 years, with bilateral cerebral palsy.

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Preschool HABIT-ILE: Study protocol for a randomised controlled trial to determine efficacy of intensive rehabilitation compared to usual care to improve motor skills of children, aged 2 to 5 years, with bilateral cerebral palsy.

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Abstract

Introduction: Young children with bilateral cerebral palsy (BCP) often experience difficulties with gross motor function, manual ability and posture, impacting developing independence in daily life activities, participation and quality of life. Hand Arm Bimanual Intensive Training Including Lower Extremity (HABIT-ILE) is a novel intensive motor intervention integrating upper and lower extremity training that has been developed and tested in older school-aged children with unilateral and BCP. This study aims to compare an adapted preschool version of HABIT-ILE to usual care in a randomised controlled trial.

Methods and analysis: 60 children with BCP aged 2-5 years, Gross Motor Function Classification System (GMFCS) II-IV will be recruited. Children will be stratified by GMFCS and randomised using concealed allocation to either receiving Preschool HABIT-ILE or usual care. Preschool HABIT-ILE will be delivered in groups of 4-6 children, for 4hrs/day for 10 days (total 40 hrs). Children receiving Preschool HABIT-ILE be provided a written home program with the aim of achieving an additional 10 hours of home practice (total dose 50 hours). Outcomes will be assessed at baseline, immediately following intervention and then retention of effects will be tested at 26 weeks. The primary outcome will be the Peabody Developmental Motors Scales–Second Edition to evaluate gross and fine motor skills. Secondary outcomes will be gross motor function (Gross Motor Function Measure-66), bimanual hand performance (Both Hands Assessment), self-care and mobility (Pediatric Evaluation of Disability Inventory-Computer Adapted Test), goal attainment (Canadian Occupational Performance Measure), global performance of daily activities (ACTIVLIM-CP), cognition and adaptive function (Behavior Rating Inventory of Executive Function®—Preschool Version), habitual physical activity (ActiGraph GT3X+) and quality of life (Infant Toddler Quality of Life Questionnaire and Child Health Utility Index-9). Analyses will follow standard principles for RCTs using two-group comparisons on all participants on an intention-to-treat basis. Comparisons between groups for primary and secondary outcomes will be conducted using regression models.

Ethics and dissemination: Ethics approval has been granted by the Medical Research Ethics Committee Children's Health Queensland Hospital and Health

Service Human Research Ethics Committee (HREC/19/QCHQ/59444) and The University of Queensland (2020000336/HREC/19/QCHQ/59444).

Trial registration number: Australian and New Zealand Clinical Trial Registry (ACTRN126200000719).

Keywords: gross motor function, manual ability, hand arm bimanual intensive training including lower extremity, pre-school age.

Word count: 5372

Article Summary

Strengths and limitations of the study

- This randomised controlled trial investigates the efficacy of an intensive motor training approach to improve gross and fine motor skills, gross motor function and manual ability for young preschool aged children (2-5 years) with bilateral cerebral palsy, powered to test both primary and secondary outcomes.
- Potential participants will be recruited from one centre in Australia over a three year period, ensuring that the sample size of 60 children across GMFCS II-IV will be met.
- Outcomes include gross and fine motor skills, gross motor function, bimanual performance, self-care, mobility, perceived performance of and satisfaction with parent/caregiver defined occupational performance goals, cognition and adaptive function, habitual physical activity and quality of life.
- A fidelity framework includes standardised training of interventionists and fidelity monitoring of each intervention camp.
- A comprehensive within trial cost-utility analysis will be conducted to synthesize the costs and benefits of the Preschool HABIT-ILE program compared to usual care.

INTRODUCTION

In Australia, cerebral palsy (CP) is the most common physical disability in childhood with an estimated 35,000 people currently living with CP.[1] In high income countries, the birth prevalence of CP is falling, with Australia reporting a reduction from 1.9 to 1.4/1000 live births between 2007 and 2012.[1] In addition to the declining rate of CP, motor severity has also reduced, as has the frequency of comorbidities such as epilepsy and intellectual impairment.[1] The total cost of CP to the Australian economy is Aus$5.17 billion dollars, equivalent to AUS$145,662 per person with CP annually which includes both the financial costs, but also those associated with lost well-being.[2]

There is no cure for CP; it is a life-long condition characterized by increasing physical disability over time.[3] Over 61% of children with CP have bilateral motor involvement, where the motor disorder impacts both legs, trunk, and for some, one or both arms.[1] Interventions that reduce the impact of physical disability resulting from CP, and promote developing independence in daily life activities, inclusion and community participation are greatly needed. A recent systematic review of interventions for preventing and treating children with CP, suggested that given the reduction in both the prevalence and severity of CP (e.g. smaller brain injuries and greater baseline motor, sensory and learning ability), children may be more likely now than ever to respond positively to motor interventions.[4]

Contemporary proven motor interventions have largely targeted school-aged children with CP and focused on upper and lower extremity motor performance separately.[4 5] To date, significant evidence exists for intensive upper extremity interventions (≈60 hours) to enhance motor performance in children with unilateral CP.[5] A number of systematic reviews[4-6] have consistently identified growing evidence for intensive motor learning based approaches to upper limb rehabilitation for children with unilateral CP (e.g. constraint induced movement therapy, Hand Arm Bimanual Intensive Training [HABIT]) to improve upper limb motor performance. Interventions to target lower compared to upper limb motor performance have generally been less intensive. A recent systematic review identified mobility and treadmill training as effective green light, “do it” interventions to improve mobility and gait[4]. One model of intervention which integrates both upper and lower limb training was developed for

children with unilateral CP. Hand Arm Bimanual Intensive Training Including Lower Extremity training (HABIT-ILE)[7-9] is based on known principles of how to induce neuroplasticity incorporating specific, intensive, repetitive task practice. Studies in basic science with animal models, have demonstrated that early intervention based on motor learning principles at critical periods of development, reverse the secondary impact of inflammation post brain injury on neuroplastic processes such as axonal growth, synaptogenesis, myelination and neurogenesis[10-12]. To date, two small trials of HABIT-ILE have been conducted, one with school aged children with unilateral CP (n=24)[8] and one for those with bilateral CP (n=20).[7] In children with bilateral CP, aged 6 to 15 years, there was a strong effect of HABIT-ILE to improve manual ability (1.6 logit increase on the ABILHAND-Kids), gross motor function (7 point increase on the Gross Motor Function Measure) and self-care (8 point increase on the Pediatric Evaluation of Disability Inventory Computer Adapted Test: PEDI-CAT).[7] A recent systematic review graded HABIT-ILE as a "yellow, probably do it" intervention, as results were promising, but require additional research to increase confidence in the estimate of treatment effect.[4] We are currently conducting a large clinical trial of HABIT-ILE for school aged children with bilateral CP to confirm and increase certainty in these results.[13]

To date, there remains a major gap in the current evidence for effective interventions for younger children (2-5yrs) with bilateral CP.[14] Children with CP reach 90% of their gross motor/movement potential by 5 years of age or younger, making the first 5 years of life a vital window of opportunity to maximize function.[15] In addition, this younger age group is less likely to have secondary complications such as muscle contractures, therefore the magnitude of outcomes possible could be larger than in older children. The current HABIT-ILE dosing schedule for school-aged children with bilateral CP (6.5 hrs/day for 10 days[13] or 6.5 hours for 13 days[7]) is not feasible to deliver to younger children. Younger children often continue to require a nap time, and are unlikely able to tolerate 6.5 hrs per day of therapy without significant fatigue, therefore a reduced dosing protocol needs to be considered. Content of therapy will differ as games will need to be carefully selected to be age appropriate to engage children and drive self-initiated mobility and bimanual hand use. An adapted dosing schedule and structure of HABIT-ILE needs to be urgently developed and evaluated

for this younger age group, to capitalize on harnessing use-dependent neuroplasticity and maximising motor function.

This pragmatic randomised controlled trial (RCT), Preschool HABIT-ILE will compare this intensive motor training approach to usual care in preschool aged children with bilateral CP (2 to 5 years) at a lower dosing schedule (50 hours) than the original HABIT-ILE studies.[8 13] This lower dose was selected as it has been shown to be acceptable, feasible and effective with a younger age group children[16] and will be augmented with a structured and written home program[17] to support families to carry out practice within their own context.

AIMS AND HYPOTHESES

Broad Aim

This RCT will be conducted in Queensland, Australia with 60 preschool aged children (2 to 5 years) with bilateral CP. This RCT with a pragmatic, single-blind design will determine if Preschool HABIT-ILE is more effective than usual care to improve gross and fine motor skills (Peabody Developmental Motor Scales – Second Edition: PDMS-2) immediately post intervention and retention at 26 weeks. Secondary outcomes will test the differential effects of Preschool HABIT-ILE compared to usual care on gross motor function (Gross Motor Function Measure 66: GMFM-66), bimanual performance (Both Hands Assessment: BoHA), self-care and mobility (PEDI-CAT), global performance of daily activities (ACTIVLIM-CP), performance of and satisfaction with parent/caregiver identified occupational performance goals (Canadian Occupational Performance Measure: COPM), executive functioning (Behavior Rating Inventory of Executive Function Preschool Version BRIEF-P), habitual physical activity (7-day free living accelerometry using ActiGraph GT3X+) and quality of life (Infant Toddler Quality of Life Questionnaire: ITQOL and the Child Health Utility Index: CHU9) immediately post intervention and retention at 26 weeks post intervention.

Primary Hypothesis

For preschool aged children with bilateral CP, Preschool HABIT-ILE for a duration of 50 hours, will be more effective than usual care to improve:

[i] gross and fine motor skills total score on the Peabody Developmental Motor Scales Second Edition (PDMS-2: difference of 7.5 Total Motor Quotient or equivalent to 0.5 standard deviation) at 3 weeks post baseline (immediately post intervention) with retention of treatment effects at 6 months post intervention.

Secondary Hypotheses

For preschool aged children with bilateral CP, Preschool HABIT-ILE for a duration of 50 hours will be more effective than a control group receiving usual care immediately post intervention and at 26 weeks post intervention to increase:

[ii] Gross motor function (GMFM-66)[18] motor capacity score;

[iii] Bimanual hand performance (BoHA)[19];

[iv] Self-care, mobility, social/cognitive and responsibility (PEDI-CAT)[20];

[v] Performance and satisfaction scores on the COPM[21];

[vi] Global performance of daily activities (ACTIVLIM-CP)[22];

[vii] Executive functioning (BRIEF-P)[23];

[viii] Quality of Life (ITQOL; and the CHU9 parent proxy)[24 25];

[ix] Cost effectiveness $(\Delta\$Cost/\Delta CP\ QOL)$ of medical treatment received.

The following hypotheses relate to objective measurement of physical activity and upper limb movement using body-worn devices including optical heart rate sensors (Polar OH1) and body-worn accelerometers (ActiGraph GT3X+):

[x] Intensity of the camp, quantified by (1) estimated energy expenditure, (2) frequency and duration of detected activities, and (3) asymmetry index between upper limbs will decrease from day 1 to day 10 of camp;

[xi] Personalized activity classification machine learning models will have >80% sensitivity and specificity to detect/classify activity type and predict intensity of physical activities in a simulated free-living environment (camp) in preschool-aged children with bilateral CP[26];

[xii] Upper limb asymmetry index on the BoHA will decrease in children receiving Preschool HABIT-ILE as compared to control;

[xiii] Minutes/day of moderate to vigorous intensity physical activity and light intensity physical activity will increase, and minutes/day of sedentary behaviour will decrease in children receiving Preschool HABIT-ILE as compared to control;

[xiv] Children receiving Preschool HABIT-ILE as compared to control will demonstrate a greater proportion of total time in ambulatory, transition and standing activities (vs sitting and lying).

METHODS

Study Design

This study is a pragmatic RCT in 60 preschool aged children with bilateral CP, which aims to evaluate the effects of Preschool HABIT-ILE (4 hrs/day for 10 days + 10 hrs home practice =total 50 hrs) compared to usual care. The study design has been informed by CONSORT Guidelines[27] (see Figure 1).

Recruitment

Sixty preschool aged children between 2 years corrected age and 5 years 11 months of age at study entry with bilateral CP confirmed by a physician will be recruited. Families with a child meeting eligibility criteria will be invited to join the study through the Queensland Children's Hospital and the Queensland Cerebral Palsy and Rehabilitation Research Centre, The University of Queensland, Brisbane Australia. Recruitment will begin following ethical and governance approvals. Recruitment will draw upon current databases within each organization, and referrals from the clinical service. We do not anticipate problems with our plan to recruit 60 children with bilateral CP as 200 children in QLD are likely to be eligible (ACPR 2018). The investigators have a strong track record of successfully completing large clinical trials, with all studies achieving recruitment targets.[28-31]

Inclusion Criteria

To be eligible for inclusion, participants must be:

(a) diagnosed with bilateral CP (diplegia/triplegia/quadriplegia: all motor types), and classified in GMFCS levels II to IV and Manual Abilities Classification System (MACS) / mini-MACS levels I-III;

(b) aged 2 to 5 years;

(c) able to grasp light objects and lift most impaired arm ≥15cm above a table surface;

(d) able to understand and follow instructions in order to complete testing and intervention.

Exclusion Criteria

(a) uncontrolled seizures in the previous 6 months (i.e. not controlled with medication as this would be a confound and/or exercise risk);
(b) Orthopaedic and/or neurological surgery in the 12 months prior to or scheduled during study period (eligible for inclusion if at least 12 months-post orthopedic and/or neurological surgery)
(c) a visual impairment interfering with treatment/testing; and
(d) unable to actively engage in the assessment process. This will be determined during screening/baseline assessment.

Randomisation

Children will be recruited in cohorts of 8-12 and stratified into 1 of 2 groups based on GMFCS (II vs. III-IV). After consent and baseline measures, children will be randomized to Preschool HABIT-ILE or control intervention through a computer-generated randomization sequence using the REDCap randomization module, determined by non-study personnel.

Blinding

All outcome assessments at each time point will be administered by experienced physiotherapists and occupational therapists. Objective measures of motor capacity (PDMS-2, BoHA, GMFM-66) will be videotaped and scored by trained raters blinded to group allocation and timing of assessments. Accelerometers will be mailed to participants to complete baseline physical activity monitoring prior to randomization. Questionnaire-based measures (ACTIVLIM-CP, ITQOL, CHU9D) will be entered directly into a secure, de-identified REDCap database or computer program (PEDI-CAT) by caregivers. Caregivers and therapists will be blinded to COPM Goal Performance and Satisfaction ratings from previous assessment timepoint/s. Following the baseline assessment and randomization, it will not be possible for participants and their caregivers to be blinded to group allocation.

Study Interventions

The Preschool HABIT-ILE and control interventions are summarised according to the Template for Intervention Description and Replication (TIDieR) Checklist[32] in Table 1.

Preschool HABIT-ILE is a motor learning approach that simultaneously addresses coordination of the upper and lower limbs.[9] Key elements of Preschool HABIT-ILE:

Dose: 40 hours of therapy achieved through a 2-week intensive group-delivered model for 4 hrs/day over 10 days (Monday to Friday) in addition to a home program for generalization of learning. Home program dose will aim to achieve a further 10 hours over the two week intervention period for a total dose of preschool HABIT-ILE of 50 hours.

Intensity: The level of intensity will be low to vigorous and will vary across the intervention session. Children will be wearing Polar OH1 Optical Heart Rate monitors during the intervention sessions which will be used in combination with accelerometry to assess intensity of physical activity.

Mode: Groups of 4-6 children (1:1 or 2:1 therapist: child ratio according to ability).

Content and tailoring: The intervention will be based on the child's motor abilities (determined at baseline), age, interests and caregiver-identified functional goals. Tasks/activities will be made incrementally more challenging. Practice will be embedded in play, using part and whole task practice with high repetition including (i) table top fine motor play-based activities; (ii) activities of daily living when sitting/standing/walking; and (iii) gross motor play. Lower extremity motor abilities and postural control will be progressed from lying to sitting on the floor and then to sitting on a small bench. Transitions will also be progressed from floor-to-sitting-to-standing.

Intervention providers: Physiotherapists and occupational therapists, who have completed standardized training and are experienced in delivering HABIT-ILE with older children will form the supervisory team overseeing delivery of Preschool HABIT-ILE. A speech pathologist will consult with the team if children have specific communication (receptive and/or expressive) or feeding difficulties. For 30 minutes, at the conclusion of each session, the child's treating therapy team will meet individually with the child's parent/caregiver/s (one-on one) and discuss the daily program and make suggestions about activities that could be practised at home. These will be detailed on a written Home Program and Practice Log completed by the caregiver. The Home Program activities will be reviewed daily by the child's treating therapy team in collaboration with the child's caregiver and updated as appropriate. Parents will be able to take short videos/photos of home practice activities on their smart phone if they wish to serve as a visual reminder for use at home. In addition, a Therapist Daily Activity Log will be completed by the therapy

team. The Therapist Daily Activity Log is a daily record detailing each activity undertaken by the child. It includes the duration and type of activity (types), position (positions), and number of repetitions or successes (for timed tasks) to assess or monitor participant adherence to the intervention. Furthermore, in combination with videotape (detailed below), logs will act as ground-truth for sensor data in order to assess accuracy and validity of activity classification.

Location: Assessments will be conducted at the Centre for Children's Health Research and Queensland Children's Hospital. The intervention will be conducted at the Queensland Paediatric Rehabilitation Service at the Queensland Children's Hospital, South Brisbane, Australia.

Following completion of the HABIT-ILE program, children will return to their usual care therapies.

Usual Care: The control group will receive usual care over the six month control period which will vary from weekly to monthly therapy. We expect that the majority of children will be accessing usual care occupational therapy and physiotherapy at an average of one session per week, funded through the National Disability Insurance Scheme. Intervention approaches will be varied and may include neurodevelopmental therapy, developmental therapy, or motor learning-based approaches. Some children may receive alternative "intensive" models of therapy as part of usual care. Families of children in each group will keep a log of usual care therapy including, frequency, duration, mode and content.

Adverse events and safety

Any minor or major adverse event associated with Preschool HABIT-ILE will be screened on a daily basis by the treating therapist and will inform the Study Coordinator and Chief Investigators (except major adverse events or those requiring medical treatment, which must be reported as soon as possible, and within 24 hours). Minor adverse events include:

- Near miss accidents (such as falling off a tricycle or falling heavily in a game)
- Sore muscles, bruises, other minor injuries not requiring medical treatment
- Feeling upset, guilty, or sad or fatigued

Major adverse events include:

- Injuries that require medical treatment (such as moderate-severe strains or broken bones)

After reporting to the site Chief Investigator, local site processes will be followed as necessary.

Fidelity

Supervisory Team: Therapist Attributes and Training

It is required that Preschool HABIT-ILE supervising therapists possess the following attributes:

- Full registration with the Australian Health Practitioner Regulation Agency (AHPRA, Physiotherapists and Occupational Therapists);
- Current Basic First Aid and Cardiac Pulmonary Resuscitation certificate;
- Evidence of immunization status (measles, mumps, rubella, pertussis, varicella, hepatitis B);
- A core group of therapists have completed standardized training in HABIT-ILE and have experience conducting a minimum of two HABIT-ILE camps with school aged children. Standardized training was provided to this core group of therapists (a minimum of one occupational therapist and one physiotherapist) employed to deliver the HABIT-ILE intervention by HABIT-ILE developer (YB). The training package includes an intervention manual and resources.

Intervention therapists/therapy students' attributes:

Delivery of the Preschool HABIT-ILE intervention will rely on volunteers including qualified physiotherapists (PT) and occupational therapists (OT) and undergraduate PT and OT therapy students. It is required that therapists/therapy students possess the following attributes:

- Full registration with the Australian Health Practitioner Regulation Agency (AHPRA, Physiotherapists and Occupational Therapists) OR evidence of enrolment in a relevant undergraduate course.
- Current Basic First Aid and Cardiac Pulmonary Resuscitation certificate;
- Evidence of immunization status.

Therapist/student Training

Onsite standardized interventionist training developed by LS, SR, YB will be provided to therapists/students by the supervisory team (LS, KM, MT) who will

deliver the intervention. This will occur in the week prior to each camp. The one day training package will include:

- Intervention manual, related publications.

Training sessions will be video recorded and accessible at any time for established or new therapists delivering the intervention. In subsequent camps, the supervisory therapists will deliver the 1-day training to students prior to the commencement of each camp.

Fidelity monitoring

Video footage will be taken for each participating child of the training and progress of tasks towards goal attainment every second day during each HABIT-ILE camp. Video footage will be reviewed by the HABIT-ILE developer (YB), with regular meetings scheduled throughout each camp to provide feedback on the intensity of delivery, and ongoing support and recommendations for treating therapists.

Screening and descriptive measures

All participants will be classified using the:

1. Mini-Manual Abilities Classification System (Mini-MACS): The Mini-MACS will classify the child's ability to hand objects in daily activities on a 5-level ordinal scale. The Mini-MACS was developed for children aged 1 to 4 years and has excellent inter-rater reliability (ICC=0.97 between therapists; 0.90 between parents and therapists.[33] The MACS will be used for children over 4 years of age.[34]
2. Gross Motor Function Classification System Expanded and Revised (GMFCS): The GMFCS classifies the child's ability to carry out self-generated movements related to sitting and walking on a 5-level ordinal scale.[35] The GMFCS has established construct validity, and good inter-rater reliability between therapists.[36]
3. Communication Function Classification System (CFCS): The CFCS will be used to classify children's everyday performance of communicating using all methods (e.g. speech, gestures, eye gaze, augmentative and alternative communication) on a five-level ordinal scale.[37] There is evidence of content validity, good test re-test reliability, good interrater reliability (0.66) between professionals.[37 38]

Two qualified, experienced occupational therapists and/or physiotherapists will perform classification at the baseline appointment and will achieve consensus by discussion.

Demographic Questionnaire: A study specific demographic questionnaire will collect information on the child's age, gender, co-morbidities, socio-economic status, family structure and supports, family income and current involvement in rehabilitation programs.

Previous medical history and assessments: Information and copies of Structural neuroimaging (sMRI at 1.5T or 3T) and history of early intervention (e.g. cooling, magnesium sulphate) will be retrieved from the child's medical records. Any sMRI will be retrieved and analysed using automated pipeline[39] and semi-quantitative scale of brain lesion severity.[40 41]

Primary outcomes

Fine and gross motor skills: The Peabody Developmental Motor Scales – Second Edition (PDMS-2)[42] will evaluate gross and fine motor skills. This standardised, norm reference measure for children from birth to 5 years of age, has been validated as a discriminative measure, and demonstrated responsiveness to change for toddlers with CP.[43]

Secondary outcomes

1. *Gross Motor Function:* Gross Motor Function Measure-66[18] (GMFM-66) is a criterion referenced observation measure developed using Rasch modelling to measure gross motor function of children with CP.[18]
2. *Bimanual Hand Performance:* Both Hands Assessment[19] (BoHA) measures how children with bilateral CP use their hands together in bimanual activities. Rasch measurement modelling showed strong evidence of internal construct validity, with two separate item difficulty hierarchies for children with: (a) symmetric upper limb use; (b) asymmetric upper limb use.[19] The test uses a selection of toys to elicit bimanual hand use in a structured play session. The BoHA takes 15 to 25 minutes to complete. The BoHA is the only available observational measure of bimanual performance validated for children with bilateral CP, MACS Levels I-III.
3. *Self-care, mobility, and social/cognitive functioning:* Pediatric Evaluation of Disability Inventory Computerised Assessment Test (PEDI-CAT): The PEDI-CAT[20]

is a Rasch analysed parent completed questionnaire which measures ability in three functional domains of daily activities (self-care), mobility, and social/cognitive and one domain for responsibility (amount of assistance provided by caregivers to their child to complete complex daily tasks) using normative standard scores and scaled scores with good validity, reliability, and standardisation with typically developing children.[20 44] The "speedy" version will be used in order to minimise participant assessment burden.

4. *Performance and satisfaction with occupational performance goals:* The Canadian Occupational Performance Measure (COPM)[21] will be used to measure performance of and satisfaction with parent/caregiver defined self-care, leisure or productivity goals. Test retest reliability is high (ICC 0.76-0.89) and the COPM is responsive to change.[21] Parents/caregivers will set up to three occupational performance goals. Perceived performance of an individualized goal and satisfaction with performance is rated on a 1-10 scale with higher scores reflecting higher perceived performance and satisfaction.
5. *Global performance in daily activities:* The ACTIVLIM-CP is a Rasch analysed parent completed questionnaire covering a range of daily activities either involving the arms or legs, or both. The questionnaire comprises 43 items on a unidimensional scale, with high reliability (R=0.98) and reproducibility (R=0.97). The questionnaire is suitable for use with children aged 2 to 18 years.[22]
6. *Range of executive function:* Behavior Rating Inventory of Executive Function®—Preschool Version (BRIEF-P) measures multiple aspects of executive functioning; scales include Inhibit, Shift, Emotional Control, Working Memory, and Plan/Organize. BRIEF-P is useful in assessing preschool-aged children (aged 2 to 5 years 11 months) with acquired neurological, and developmental conditions.[23] A single rating form allows parents to rate a child's executive functions within the context of his or her everyday environments. BRIEF-P Demonstrates high internal consistency reliability (0.80-0.95 for the parent sample and moderate test-retest reliability (0.78-0.90).[23]
7. *Objectively measured physical activity and upper limb movement:* The ActiGraph GT3X+ is a small (4.6cm x 3.3cm x 1.5cm) light weight (19g) triaxial accelerometer which provides valid assessments of habitual physical activity and bimanual performance in children with CP.[45 46] During the three assessment timepoints, one ActiGraph GT3X+ will be worn on each wrist, one additional

ActiGraph GT3X+ will be worn on the less-affected thigh, and one Polar OH1 Optical HR Monitor will be worn on one upper arm during PDMS-2, BoHA, and GMFM-66 assessments. One week prior to each assessment time point, two ActiGraphs (1 less-affected thigh, 1 less-affected wrist) will also be worn in the participant's usual daily life at home (free living) for 7 days during all waking hours at each time-point to assess habitual physical activity. During this time, parents will complete a log book to record their child's activity and position throughout each day. Throughout the 10 day HABIT-ILE intervention, children will wear one ActiGraph GT3X+ on each wrist and on the less-affected thigh, and one Polar OH1 Optical HR Monitor on one upper arm. Data will be processed using count-based methods to objectively quantify change in bimanual performance (asymmetry index) on the BoHA.[45] The intensity/type of practice during the camp, intensity of free-living habitual physical activity, and time spent ambulatory, transitioning and standing (vs sitting and lying) will be determined using machine learning approaches. HR and inertial data during assessments and camp will enable (1) testing of existing machine-learning models for activity classification,[26] (2) development of personalized machine-learning models which are hypothesized to be more accurate,[26] (3) quantification of the intensity and type of practice during the camp, (4) objective measurement of change in intensity and type of physical activity. Videotapes of therapy sessions and assessments will be used alongside the Therapist Daily Activity Logs as ground-truth for sensor data classification accuracy and validity analysis.

8. *Quality of life:* The Infant Toddler Quality of Life Questionnaire (ITQOL) is designed for infants aged 2 months to 5 years of age.[24] The ITQOL comprises 97 items, with good evidence for discriminative validity and reliability.[47] The Child Health Utility Index (CHU9)[25] is a paediatric health related quality of life measure for use in economic evaluation along with a specifically design Health Resource Use (HRU) questionnaire. The measure consists of nine questions. In this study, the CHU9 will be completed by the child's primary caregiver.

Data Management

Data types:

We will collect objective data on fine and gross motor skills using the PDMS-2, gross motor function using the GMFM-66, bimanual hand performance using the BoHA, and objective physical activity and upper limb movement related to energy

expenditure (Accelerometers and HR monitors). All measures are suitable for children 2 to 5 years of age with bilateral CP. Information collected from the child's primary caregiver includes: two questionnaire-based measures of self-care, mobility and global performance (PEDI-CAT, ACTIVLIM-CP), one questionnaire measuring cognition and adaptive function (BRIEF-P), three questionnaires assessing their child's quality of life (ITQOL, CHU9) and health resource use (HRU) which will be used for the health economic analysis. All data will be re-identifiable.

Data collection:

Data will be collected in one of four ways: (1) paper forms; (2) online survey platform (REDCap) instead of/in addition to paper forms; (3) devices (photo/video/audio recording devices and ActiGraph GT3X+, Polar OH1) ; or (4) face-to-face assessments with the child. All information will be coded with a participant ID number with any identification of codes (e.g. consent forms and other identifiable information) will be stored in a separate location. All data will be stored in electronic form on the Queensland Cerebral Palsy and Rehabilitation Research Centre, The University of Queensland secure server and REDCap (database) on secure Australian servers. Access to data will be limited to chief investigators and study coordinators as approved by the relevant ethics committees. Data management will comply with relevant privacy protocols, such as the Australian Standard on personal privacy protection.

Management of withdrawals

Participants can withdraw at any time with no penalty. Participants are informed of their right to withdraw at any time without consequences at the time of reading participant information forms and signing of consent forms. Participants that withdraw will not be replaced, as the a priori power calculation will account for a 20% dropout rate.

Sample Size Estimation

Based on a difference of 7.5 PDMS-2 Motor Quotients, with an alpha of 5% and 80% power, assuming a standard deviation of 9.2 and buffering for 20% attrition, a sample size of 60 will be required.[48] We will have 88% power to detect a difference of 5 points or greater on the GMFM-66 (assuming SD=6) and alpha=0.05.

Statistical Analysis

Analyses will follow standard principles for RCTs using two-group comparisons on all participants on an intention-to-treat basis. Primary comparison immediately post

intervention (T2) based on PDMS-2 Total Motor Quotient scores will be between treatment groups using linear regression with treatment group (Preschool HABIT-ILE/control) included as the main effect and baseline PDMS-2 Motor Quotient as the covariable. Effect estimates will be presented as mean difference and 95% confidence interval. We will use similar methods to compare outcomes between groups immediately post intervention (T2) and at 6 months post intervention (T3) for gross motor function, bimanual hand function, self-care, mobility, global performance of daily activities, performance of and satisfaction with occupational performance goals, executive function and quality of life. In cases where interval data are not able to be transformed appropriately for regression analyses, non-parametric methods (Mann-Whitney U) will be used for between-treatment comparisons.

Health Economics

A within trial economic evaluation will be conducted to estimate the costs and outcomes of the Preschool HABIT-ILE therapy program. Resource utilization (staff time, equipment and facility use) associated with the delivery of the program will be collected alongside the RCT. Health care utilization will be assessed using a resource use questionnaire previously used in CP child and HABIT-ILE studies.[13 49] Utility will be derived from the CHU-9D[25], a generic child quality of life measure designed specifically for economic evaluation and which has been validated in an Australian population.[50] Incremental Cost Effectiveness Ratios (ICERs) will be estimated and where appropriate sensitivity analyses undertaken as in previous RCTs by our group.[51]

Ethics and dissemination

Full ethical approval has been granted by the Children's Health Queensland Hospital and Health Service Human Research Ethics Committee (HREC/19/QCHQ/59444), the Medical Research Ethics Committee of The University of Queensland (2020000336/HREC/19/QCHQ/59444). Participant information and consent forms will be provided to all participants and their caregivers prior to entering the study. Full written and informed consent will be obtained from all caregivers of children participating in the trial. The trial has been registered with the Australian and New Zealand Clinical Trial Registry (ACTRN126200000719p). This protocol is reported according to the Standard Protocol Items: Recommendations for Intervention Trials statement (SPIRIT)[52] and Template for Intervention Description and Replication Checklist (TIDieR).[32]

Findings will be disseminated via peer reviewed publication of study results, newsletter feedback to consumers and presentation at key national and international conferences. The authors will plan a knowledge translation pathway if the intervention proves effective in improving motor abilities of preschool aged children with bilateral CP.

Public/Patient Involvement Statement

Preschool HABIT-ILE was trialled in a truncated format in September 2019 (3 hours/day, 3 days/week for 1 week) with two participants (aged 3, GMFCS III and aged 5, GMFCS IV). Parents provided ongoing daily feedback on the feasibility and acceptability of Preschool HABIT-ILE, and confirmed our planned dosing schedule for the subsequent RCT. Participants and their families will be informed of progress and outcomes of this study via newsletter and conferences open to consumers.

DISCUSSION

Young children with CP reach 90% of their gross motor/movement potential by five years or younger.[15] Sixty percent of children with CP have a bilateral presentation of movement difficulties, yet there is limited evidence for effective interventions to improve their gross motor and manual abilities[53]. Building on a previous small study[49] and our current HABIT-ILE Australia project[13], we aim to test the efficacy of an adapted protocol for younger children aged 2 to 5 years with bilateral CP to improve motor outcomes. One potential limitation of the study is that therapy students under the supervision of trained therapists will be primarily delivering the Preschool HABIT-ILE intervention. As we have done in the larger HABIT-ILE Australia study, we will account for this by providing one day of standardized training for all interventionists, daily debriefing meetings at the end of each day, and ongoing daily feedback from supervising therapists. Secondly, the dose being tested (50 hours) was a pragmatic choice based on what is likely to be feasible and acceptable in the Australian context. This dose, however, relies on 10 hours of home practice. We will follow evidence-based processes for the development, delivery and support of parents and caregivers in the implementation of home practice.[17] Usual care is highly variable and may not be at an equivalent dose as the intended Preschool HABIT-ILE. It is not possible to standardize usual care given it is delivered by many different service providers under pre-agreed funding packages. We will however, comprehensively record the type and dose of standard care to determine any

differences in dosing schedules and content of intervention. Our inclusion of children classified GMFCS II to IV with all motor types aims to ensure that results are generalizable, however if there is a large differential response to the intervention, the study may be underpowered.

The study has a number of strengths. The number of participants to be included has been calculated for the primary clinical outcome and recruitment is feasible. Selected outcome measures have evidence for both validity and reliability in our population of interest. Standardized interventionist training and fidelity monitoring already developed in our HABIT-ILE Australia[10] study will be adapted, in addition to a with-in trial cost-utility analysis will provide vital information to inform the potential translation of this intervention, particularly in Australia under the National Disability Insurance Scheme. It is anticipated that results of this RCT will be disseminated widely through peer reviewed journals and academic conferences.

Figure 1. Participant flow diagram for Preschool HABIT-ILE.

Trial Status Update

The study was temporarily paused due to COVID-19. Recruitment has commenced in October 2020 and anticipated commencement of the intervention is in March 2021. A 12 month no cost extension on the grant funding this project has been provided.

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Competing Interests: None declared

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Author Contributions

LS is the chief investigator together with KM, YB and MT developed the intervention protocol. LS, RB, SR, MT and KM designed, established and achieved funding for this study. LS and SR are responsible for ethics applications and reporting. LS, KM, MT, AB, SR are responsible for recruitment and data collection. LS, SR, MT and KM are responsible for implementation of the interventionist training and fidelity monitoring. SR, ST, MA developed the protocol for evaluation of physical activity and upper limb movement. LS, KM, MT, SR, AB will take the lead roles on preparation for publication of the clinical outcomes; DR, LS and RB will take lead roles of preparation of health economic publications. MC will provide biostatistical advice and oversight for all analyses and publications. LS and the chief investigators drafted the final version of this manuscript. All authors have contributed to the writing and critical review of the manuscript and have approved the final version. All data from this study will be submitted to peer review journals.

Table 1: TIDieR checklist[32] Comparison between Preschool HABIT-ILE and traditional "usual care" intervention

Item	Experimental Preschool HABIT-ILE	Control "usual care"
Name	Preschool Hand Arm Bimanual Intensive Training Including Lower Extremity	Traditional eclectic usual care
Why	Rationale: Intense, repetitive, active motor learning induces activity dependent neuroplasticity. Essential elements: a. Goal directed (goals defined by child/caregiver) b. Motor training with concurrent challenge for upper and lower limbs and posture c. Shaping d. Active practice of goals e. High repetition and intensity	Rationale: Usual care is highly variable, and may be based on biomechanical, neurodevelopmental, or motor learning principles. Elements may include: a. Goals defined by either caregiver OR therapist b. Stretching, splinting, casting c. Focus on developmental milestones d. Therapist physically facilitates more typical (normal) movement patterns with children who may be passive recipients e. May involve active goal practice using motor learning principles f. Equipment prescription
Materials	Therapy bench, fit ball to intensely and repeatedly challenge posture; developmentally appropriate	Splints, casts, adaptive equipment to compensate for tasks child cannot perform.

	activities/toys/games for children to actively develop bimanual hand skills with continuous practice of part and whole tasks through play. Whole task practice of individually identified functional goals with specific materials related to each goal.	
Who	Therapy students (physiotherapy, occupational therapy, exercise science), volunteer physiotherapists and occupational therapists working directly with child with a ratio of 2:1 interventionists/child. Experienced physiotherapists and occupational therapists who have completed standardised training in HABIT-ILE will supervise and mentor interventionists.	Occupational therapist and/or physiotherapist with the child and parents.
How	Clinic setting	Clinic, hospital, home or day care, preschool setting
How Much	4 hours/day for 10 weekdays over a 2 week period (total 40 hours) + home program for 10 hours over 2 weeks for a total dose of 50 hours	Weekly, monthly therapist provided ± home program. Highly variable. Some children may have access to other variations of intensive therapy interventions.
Tailoring	Tailored to the child's individually defined functional goals. Daily review of progress with a view to continually and incrementally increase the challenge	Highly variable.

How well	Daily video footage of participants at the day camp will be taken and reviewed by the supervising team every second to third day to ensure delivery of intervention as per protocol.	Detailed survey of parents about intervention approaches used.

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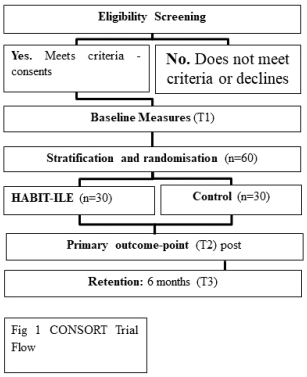

Figure 1. CONSORT Flow Chart

451x254mm (72 x 72 DPI)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1

Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	
Protocol version	#3	Date and version identifier	footer
Funding	#4	Sources and types of financial, material, and other support	21
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1, 21-22
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	21-22
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and	21-22

		other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	6-7
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	6-7
Objectives	#7	Specific objectives or hypotheses	8
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	9-10
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	12

Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	10
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	11-12
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	18
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	13-14
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	13
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	15-17

Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Consort flow chart
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	18-19
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	10-11
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	10
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque,	10

		sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	10
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	10
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	-
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	14-17

Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	18
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	18
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	19
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	19
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	19
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and	NA

		competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	13
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	-
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	19
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	19-20

Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	19-20
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	11, 18
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	21
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	18
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	19-20

Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	