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Preschool HABIL-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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3 **Preschool HABIL-ILE: A randomised controlled trial to determine**
4 **efficacy of intensive rehabilitation compared to usual care to**
5 **improve motor skills of children, aged 2 to 5 years, with bilateral**
6 **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).

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3 **Keywords:** cerebral palsy, children, gross motor function, manual ability,
4 randomised controlled trial, hand arm bimanual intensive training including lower
5 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.
- 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 reviews⁴⁻⁶ 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 gait⁴. One model of intervention which integrates both upper and lower limb training was developed for

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3 children with unilateral CP. Hand Arm Bimanual Intensive Training Including Lower
4 Extremity training (HABIT-ILE)⁷⁻⁹ is based on known principles of how to induce
5 neuroplasticity incorporating specific, intensive, repetitive task practice. To date, two
6 small trials of HABIT-ILE have been conducted, one with school aged children with
7 unilateral CP (n=24)⁸ and one for those with bilateral CP (n=20).⁷ In children with
8 bilateral CP, aged 6 to 15 years, there was a strong effect of HABIT-ILE to improve
9 manual ability (1.6 logit increase on the ABILHAND-Kids), gross motor function (7
10 point increase on the Gross Motor Function Measure) and self-care (8 point increase
11 on the Pediatric Evaluation of Disability Inventory Computer Adapted Test: PEDI-
12 CAT).⁷ A recent systematic review graded HABIT-ILE as a “yellow, probably do it”
13 intervention, as results were promising, but require additional research to increase
14 confidence in the estimate of treatment effect.⁴ We are currently conducting a large
15 clinical trial of HABIT-ILE for school aged children with bilateral CP to confirm and
16 increase certainty in these results.¹⁰
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29 To date, there remains a major gap in the current evidence for effective interventions
30 for younger children (2-5yrs) with bilateral CP.¹¹ Children with CP reach 90% of their
31 gross motor/movement potential by 5 years of age or younger, making the first 5
32 years of life a vital window of opportunity to maximize function.¹² In addition, this
33 younger age group is less likely to have secondary complications such as muscle
34 contractures, therefore the magnitude of outcomes possible could be larger than in
35 older children. The current HABIT-ILE dosing schedule for school-aged children with
36 bilateral CP (6.5 hrs/day for 10 days¹⁰ or 6.5 hours for 13 days⁷) is not feasible to
37 deliver to younger children. Content of therapy will differ as games will need to be
38 carefully selected to be age appropriate to engage children and drive self-initiated
39 mobility and bimanual hand use. An adapted dosing schedule and structure of
40 HABIT-ILE needs to be urgently developed and evaluated for this younger age
41 group, to capitalize on harnessing use-dependent neuroplasticity and maximising
42 motor function.
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55 This pragmatic randomised controlled trial (RCT), Preschool HABIT-ILE will compare
56 this intensive motor training approach to usual care in preschool aged children with
57 bilateral CP (2 to 5 years) at a lower dosing schedule (50 hours) than the original
58 HABIT-ILE studies.^{8 10} This lower dose was selected as it has been shown to be
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3 acceptable, feasible and effective with a younger age group children¹³ and will be
4 augmented with a structured and written home program¹⁴ to support families to carry
5 out practice within their own context.
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10 **AIMS AND HYPOTHESES**

11 **Broad Aim**

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

44 For preschool aged children with bilateral CP, Preschool HABIL-ILE for a duration of
45 50 hours, will be more effective than a control group receiving usual care to improve:
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48 [i] gross and fine motor skills total score on the Peabody Developmental Motor
49 Scales Second Edition (PDMS-2: difference of 7.5 Total Motor Quotient or equivalent
50 to 0.5 standard deviation) at 3 weeks immediately post intervention with retention of
51 treatment effects at 6 months post intervention.
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56 **Secondary Hypotheses**

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3 For preschool aged children with bilateral CP, Preschool HABIT-ILE for a duration of
4 50 hours will be more effective than a control group receiving usual care immediately
5 post intervention and at 26 weeks post intervention to increase:
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8 [ii] Gross motor function (GMFM-66)¹⁵ motor capacity score;

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

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

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14 [v] Performance and satisfaction scores on the COPM¹⁸;

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

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

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

21
22 [ix] Cost effectiveness ($\Delta\$Cost/\Delta CP\ QOL$) of medical treatment received.

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24 The following hypotheses relate to objective measurement of physical activity and
25 upper limb movement using body-worn devices including optical heart rate sensors
26 (Polar OH1) and body-worn accelerometers (ActiGraph GT3X+):
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28 [x] Intensity of the camp, quantified by (1) estimated energy expenditure, (2)
29 frequency and duration of detected activities, and (3) asymmetry index between
30 upper limbs will decrease from day 1 to day 10 of camp;

31 [xi] Personalized activity classification machine learning models will have >80%
32 sensitivity and specificity to detect/classify activity type and predict intensity of
33 physical activities in a simulated free-living environment (camp) in preschool-aged
34 children with bilateral CP²³;

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

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

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

46 Study Design

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3 This study is a pragmatic RCT in 60 preschool aged children with bilateral CP, which
4 aims to evaluate the effects of Preschool HABIT-ILE (4 hrs/day for 10 days + 10 hrs
5 home practice =total 50 hrs) compared to usual care. The study design has been
6 informed by CONSORT Guidelines²⁴ (see Figure 1).
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10 **Recruitment**

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

32 To be eligible for inclusion, participants must be:

- 33 (a) diagnosed with bilateral CP (diplegia/triplegia/quadruplegia: all motor types),
34 GMFCS II to IV;
- 35 (b) aged 2 to 5 years;
- 36 (c) able to grasp light objects and lift most impaired arm ≥ 15 cm above a table
37 surface;
- 38 (d) able to understand and follow instructions in order to complete testing.
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45 *Exclusion Criteria*

- 46 (a) uncontrolled seizures in the previous 6 months (i.e. not controlled with
47 medication as this would be a confound and/or exercise risk);
- 48 (b) Orthopaedic and/or neurological surgery in the 12 months prior to or
49 scheduled during study period (eligible for inclusion if at least 12 months-post
50 orthopedic and/or neurological surgery)
- 51 (c) a visual impairment interfering with treatment/testing; and
- 52 (d) unable to actively engage in the assessment process. This will be determined
53 during screening/baseline assessment.
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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) Checklist²⁹ 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.

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3 *Mode:* Groups of 4-6 children (1:1 or 2:1 therapist: child ratio according to ability).
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5 *Content and tailoring:* The intervention will be based on the child's motor abilities
6 (determined at baseline), age, interests and caregiver-identified functional goals.
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8 Tasks/activities will be made incrementally more challenging. Practice will be
9 embedded in play, using part and whole task practice with high repetition including (i)
10 table top fine motor play-based activities; (ii) activities of daily living when
11 sitting/standing/walking; and (iii) gross motor play. Lower extremity motor abilities
12 and postural control will be progressed from lying to sitting on the floor and then to
13 sitting on a small bench. Transitions will also be progressed from floor-to-sitting-to-
14 standing.
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21 *Intervention providers:* Physiotherapists and occupational therapists, who have
22 completed standardized training and are experienced in delivering HABIT-ILE with
23 older children will form the supervisory team overseeing delivery of Preschool
24 HABIT-ILE. A speech pathologist will consult with the team if children have specific
25 communication (receptive and/or expressive) or feeding difficulties. For 30 minutes,
26 at the conclusion of each session, the child's treating therapy team will meet
27 individually with the child's parent/caregiver/s (one-on one) and discuss the daily
28 program and make suggestions about activities that could be practised at home.
29 These will be detailed on a written Home Program and Practice Log completed by
30 the caregiver. The Home Program activities will be reviewed daily by the child's
31 treating therapy team in collaboration with the child's caregiver and updated as
32 appropriate. Parents will be able to take short videos/photos of home practice
33 activities on their smart phone if they wish to serve as a visual reminder for use at
34 home. In addition, a Therapist Daily Activity Log will be completed by the therapy
35 team. The Therapist Daily Activity Log is a daily record detailing each activity
36 undertaken by the child. It includes the duration and type of activity (types), position
37 (positions), and number of repetitions or successes (for timed tasks) to assess or
38 monitor participant adherence to the intervention. Furthermore, in combination with
39 videotape (detailed below), logs will act as ground-truth for sensor data in order to
40 assess accuracy and validity of activity classification.
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56 *Location:* Assessments will be conducted at the Centre for Children's Health
57 Research and Queensland Children's Hospital. The intervention will be conducted at
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3 the Queensland Paediatric Rehabilitation Service at the Queensland Children's
4 Hospital, South Brisbane, Australia.

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

22 23 **Adverse events and safety**

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

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

32 Major adverse events include:

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

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

37 **Fidelity**

38 Supervisory Team: Therapist Attributes

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

- 41 • Full registration with the Australian Health Practitioner Regulation Agency
42 (AHPRA, Physiotherapists and Occupational Therapists);
- 43 • 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

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3 excellent inter-rater reliability (ICC=0.97 between therapists; 0.90 between
4 parents and therapists).³⁰

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

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

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32 Previous medical history and assessments: Information and copies of Structural
33 neuroimaging (sMRI at 1.5T or 3T) and history of early intervention (e.g. cooling,
34 magnesium sulphate) will be retrieved from the child's medical records. Any sMRI
35 will be retrieved and analysed using automated pipeline³⁵ and semi-quantitative
36 scale of brain lesion severity.^{36 37}

41 **Primary outcomes**

42
43 *Fine and gross motor skills:* The Peabody Developmental Motor Scales – Second
44 Edition (PDMS-2)³⁸ will evaluate gross and fine motor skills. This standardised, norm
45 reference measure for children from birth to 5 years of age, has been validated as a
46 discriminative measure, and demonstrated responsiveness to change for toddlers
47 with CP.³⁹

51 **Secondary outcomes**

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54 1. *Gross Motor Function:* Gross Motor Function Measure-66¹⁵ (GMFM-66) is a
55 criterion referenced observation measure developed using Rasch modelling to
56 measure gross motor function of children with CP.¹⁵
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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-CAT¹⁷ 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

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3 single rating form allows parents to rate a child's executive functions within the
4 context of his or her everyday environments. BRIEF-P Demonstrates high internal
5 consistency reliability (0.80-0.95 for the parent sample and moderate test-retest
6 reliability (0.78-0.90).²⁰
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11 7. *Objectively measured physical activity and upper limb movement:* The ActiGraph
12 GT3X+ is a small (4.6cm x 3.3cm x 1.5cm) light weight (19g) triaxial
13 accelerometer which provides valid assessments of habitual physical activity and
14 bimanual performance in children with CP.^{41 42} During the three assessment
15 timepoints, one ActiGraph GT3X+ will be worn on each wrist, one additional
16 ActiGraph GT3X+ will be worn on the less-affected thigh, and one Polar OH1
17 Optical HR Monitor will be worn on one upper arm during PDMS-2, BoHA, and
18 GMFM-66 assessments. One week prior to each assessment time point, two
19 ActiGraphs (1 less-affected thigh, 1 less-affected wrist) will also be worn in the
20 participant's usual daily life at home (free living) for 7 days during all waking hours
21 at each time-point to assess habitual physical activity. Throughout the 10 day
22 HABIT-ILE intervention, children will wear one ActiGraph GT3X+ on each wrist
23 and on the less-affected thigh, and one Polar OH1 Optical HR Monitor on one
24 upper arm. Data will be processed using count-based methods to objectively
25 quantify change in bimanual performance (asymmetry index) on the BoHA.⁴¹ The
26 intensity/type of practice during the camp, intensity of free-living habitual physical
27 activity, and time spent ambulatory, transitioning and standing (vs sitting and
28 lying) will be determined using machine learning approaches. HR and inertial data
29 during assessments and camp will enable (1) testing of existing machine-learning
30 models for activity classification,²³ (2) development of personalized machine-
31 learning models which are hypothesized to be more accurate,²³ (3) quantification
32 of the intensity and type of practice during the camp, (4) objective measurement of
33 change in intensity and type of physical activity. Videotapes of therapy sessions
34 and assessments will be used alongside the Therapist Daily Activity Logs as
35 ground-truth for sensor data classification accuracy and validity analysis.
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53 8. *Quality of life:* The Infant Toddler Quality of Life Questionnaire (ITQOL) is
54 designed for infants aged 2 months to 5 years of age.²¹ The ITQOL comprises 97
55 items, with good evidence for discriminative validity and reliability.⁴³ The Child
56 Health Utility Index (CHU9)²² is a paediatric health related quality of life measure
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3 for use in economic evaluation. The measure consists of nine questions. In this
4 study, the CHU9 will be completed by the child's primary caregiver.

6 **Data Management**

8 **Data types:**

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

27 **Data collection:**

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

50 **Management of withdrawals**

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

60 **Sample Size Estimation**

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

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

35 A within trial economic evaluation will be conducted to estimate the costs and
36 outcomes of the Preschool HABIT-ILE therapy program. Resource utilization (staff
37 time, equipment and facility use) associated with the delivery of the program will be
38 collected alongside the RCT. Health care utilization will be assessed using a
39 resource use questionnaire previously used in CP child and HABIT-ILE studies.^{10 45}
40 Utility will be derived from the CHU-9D²², a generic child quality of life measure
41 designed specifically for economic evaluation and which has been validated in an
42 Australian population.⁴⁶ Incremental Cost Effectiveness Ratios (ICERs) will be
43 estimated and where appropriate sensitivity analyses undertaken as in previous
44 RCTs by our group.⁴⁷
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53 **Ethics and dissemination**

54 Full ethical approval has been granted by the Children's Health Queensland Hospital
55 and Health Service Human Research Ethics Committee (HREC/19/QCHQ/59444),
56 the Medical Research Ethics Committee of The University of Queensland
57 (2020000336/HREC/19/QCHQ/59444). Participant information and consent forms
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3 will be provided to all participants and their caregivers prior to entering the study. Full
4 written and informed consent will be obtained from all caregivers of children
5 participating in the trial. The trial has been registered with the Australian and New
6 Zealand Clinical Trial Registry (ANZCTR: 12620000071921). This protocol is
7 reported according to the Standard Protocol Items: Recommendations for
8 Intervention Trials statement (SPIRIT)⁴⁸ and Template for Intervention Description
9 and Replication Checklist (TIDieR).²⁹

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

15 **Public/Patient Involvement Statement**

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

22 **DISCUSSION**

23 Young children with CP reach 90% of their gross motor/movement potential by five
24 years or younger.¹² Sixty percent of children with CP have a bilateral presentation of
25 movement difficulties, yet there is limited evidence for effective interventions to
26 improve their gross motor and manual abilities. Building on a previous small study⁴⁹
27 and our current HABIT-ILE Australia project¹⁰, we aim to test the efficacy of an
28 adapted protocol for younger children aged 2 to 5 years with bilateral CP to improve
29 motor outcomes. One potential limitation of the study is that therapy students under
30 the supervision of trained therapists will be primarily delivering the Preschool HABIT-
31 ILE intervention. As we have done in the larger HABIT-ILE Australia study, we will
32 account for this by providing one day of standardized training for all interventionists,
33 daily debriefing meetings at the end of each day, and ongoing daily feedback from
34 supervising therapists. Secondly, the dose being tested (50 hours) was a pragmatic
35 choice based on what is likely to be feasible and acceptable in the Australian
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3 context. This dose, however, relies on 10 hours of home practice. We will follow
4 evidence-based processes for the development, delivery and support of parents and
5 caregivers in the implementation of home practice.¹⁴
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10 The study has a number of strengths. The number of participants to be included has
11 been calculated for the primary clinical outcome and recruitment is feasible.
12 Selected outcome measures have evidence for both validity and reliability in our
13 population of interest. Standardized interventionist training and fidelity monitoring
14 already developed in our HABIT-ILE Australia¹⁰ study will be adapted, in addition to a
15 with-in trial cost-utility analysis will provide vital information to inform the potential
16 translation of this intervention, particularly in Australia under the National Disability
17 Insurance Scheme. It is anticipated that results of this RCT will be disseminated
18 widely through peer reviewed journals and academic conferences.
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27 Figure 1. Participant flow diagram for Preschool HABIT-ILE.
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30 **Acknowledgments**

31 We acknowledge Sarah Goodman and Dr Natalie Dos Santos, Study Clinical
32 Research Coordinators and the Queensland Paediatric Rehabilitation Service,
33 Queensland Children's Hospital for their support of the project.
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36 **Competing Interests:** None declared
37

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41 Fellowship (RB, 1105038). Australian Government Research Training scholarship
42 (AB), Children Hospital Foundation – Lola Hughes Efsthathis Top-Up scholarship (AB)
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48 **Author Contributions**

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

Table 1: TIDieR checklist²⁹ 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	<p>Rationale: Intense, repetitive, active motor learning induces activity dependent neuroplasticity.</p> <p>Essential elements:</p> <ol style="list-style-type: none"> 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 	<p>Rationale: Usual care is highly variable, and may be based on biomechanical, neurodevelopmental, or motor learning principles.</p> <p>Elements may include:</p> <ol style="list-style-type: none"> 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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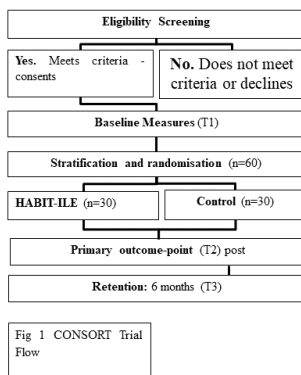


Figure 1. CONSORT Flow Chart

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 SPIRIT reporting guidelines, and cite them as:

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

1	Trial registration	#2a	Trial identifier and registry name. If not yet registered,	4
2			name of intended registry	
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6	Trial registration:	#2b	All items from the World Health Organization Trial	
7			Registration Data Set	
8	data set			
9				
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12	Protocol version	#3	Date and version identifier	footer
13				
14				
15	Funding	#4	Sources and types of financial, material, and other	21
16			support	
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20	Roles and	#5a	Names, affiliations, and roles of protocol contributors	1, 21-22
21				
22	responsibilities:			
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24	contributorship			
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28	Roles and	#5b	Name and contact information for the trial sponsor	1
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30	responsibilities:			
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32	sponsor contact			
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34	information			
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38	Roles and	#5c	Role of study sponsor and funders, if any, in study	21-22
39			design; collection, management, analysis, and	
40	responsibilities:		interpretation of data; writing of the report; and the	
41			decision to submit the report for publication, including	
42	sponsor and funder		whether they will have ultimate authority over any of	
43			these activities	
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52	Roles and	#5d	Composition, roles, and responsibilities of the	21-22
53			coordinating centre, steering committee, endpoint	
54	responsibilities:		adjudication committee, data management team, and	
55				
56	committees			
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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

1	Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If	10
2			applicable, eligibility criteria for study centres and	
3			individuals who will perform the interventions (eg,	
4			surgeons, psychotherapists)	
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11	Interventions:	#11a	Interventions for each group with sufficient detail to allow	11-12
12			replication, including how and when they will be	
13	description		administered	
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19	Interventions:	#11b	Criteria for discontinuing or modifying allocated	18
20			interventions for a given trial participant (eg, drug dose	
21	modifications		change in response to harms, participant request, or	
22			improving / worsening disease)	
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29	Interventions:	#11c	Strategies to improve adherence to intervention	13-14
30			protocols, and any procedures for monitoring adherence	
31	adherence		(eg, drug tablet return; laboratory tests)	
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36	Interventions:	#11d	Relevant concomitant care and interventions that are	13
37			permitted or prohibited during the trial	
38	concomitant care			
39				
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41				
42	Outcomes	#12	Primary, secondary, and other outcomes, including the	15-17
43			specific measurement variable (eg, systolic blood	
44			pressure), analysis metric (eg, change from baseline,	
45			final value, time to event), method of aggregation (eg,	
46			median, proportion), and time point for each outcome.	
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53			Explanation of the clinical relevance of chosen efficacy	
54			and harm outcomes is strongly recommended	
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1	Participant timeline	#13	Time schedule of enrolment, interventions (including any	Consort
2			run-ins and washouts), assessments, and visits for	flow
3			participants. A schematic diagram is highly	chart
4			recommended (see Figure)	
5				
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10				
11	Sample size	#14	Estimated number of participants needed to achieve	18-19
12			study objectives and how it was determined, including	
13			clinical and statistical assumptions supporting any	
14			sample size calculations	
15				
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21	Recruitment	#15	Strategies for achieving adequate participant enrolment	10-11
22			to reach target sample size	
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24				
25				
26	Methods:			
27				
28	Assignment of			
29	interventions (for			
30	controlled trials)			
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36	Allocation: sequence	#16a	Method of generating the allocation sequence (eg,	10
37	generation		computer-generated random numbers), and list of any	
38			factors for stratification. To reduce predictability of a	
39			random sequence, details of any planned restriction (eg,	
40			blocking) should be provided in a separate document that	
41			is unavailable to those who enrol participants or assign	
42			interventions	
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53	Allocation	#16b	Mechanism of implementing the allocation sequence (eg,	10
54	concealment		central telephone; sequentially numbered, opaque,	
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58	mechanism			
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sealed envelopes), describing any steps to conceal the sequence until interventions are assigned

Allocation: [#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): [#17b](#) If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial -

emergency unblinding

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

1	Data collection plan:	#18b	Plans to promote participant retention and complete	18
2				
3	retention		follow-up, including list of any outcome data to be	
4			collected for participants who discontinue or deviate from	
5			intervention protocols	
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11	Data management	#19	Plans for data entry, coding, security, and storage,	18
12			including any related processes to promote data quality	
13			(eg, double data entry; range checks for data values).	
14			Reference to where details of data management	
15			procedures can be found, if not in the protocol	
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23	Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary	19
24			outcomes. Reference to where other details of the	
25			statistical analysis plan can be found, if not in the	
26			protocol	
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33	Statistics: additional	#20b	Methods for any additional analyses (eg, subgroup and	19
34	analyses		adjusted analyses)	
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39	Statistics: analysis	#20c	Definition of analysis population relating to protocol non-	19
40	population and		adherence (eg, as randomised analysis), and any	
41	missing data		statistical methods to handle missing data (eg, multiple	
42			imputation)	
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48	Methods: Monitoring			
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51	Data monitoring:	#21a	Composition of data monitoring committee (DMC);	NA
52	formal committee		summary of its role and reporting structure; statement of	
53			whether it is independent from the sponsor and	
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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

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11	Data monitoring:	#21b	Description of any interim analyses and stopping
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13	interim analysis		guidelines, including who will have access to these
14			
15			interim results and make the final decision to terminate
16			
17			the trial
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20	Harms	#22	Plans for collecting, assessing, reporting, and managing
21			
22			solicited and spontaneously reported adverse events and
23			
24			other unintended effects of trial interventions or trial
25			
26			conduct
27			
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30	Auditing	#23	Frequency and procedures for auditing trial conduct, if
31			
32			any, and whether the process will be independent from
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34			investigators and the sponsor
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38	Ethics and		
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40	dissemination		
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43	Research ethics	#24	Plans for seeking research ethics committee /
44			
45	approval		institutional review board (REC / IRB) approval
46			
47			
48	Protocol	#25	Plans for communicating important protocol modifications
49			
50	amendments		(eg, changes to eligibility criteria, outcomes, analyses) to
51			
52			relevant parties (eg, investigators, REC / IRBs, trial
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54			participants, trial registries, journals, regulators)
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1	Consent or assent	#26a	Who will obtain informed consent or assent from potential	19-20
2			trial participants or authorised surrogates, and how (see	
3			Item 32)	
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9	Consent or assent:	#26b	Additional consent provisions for collection and use of	NA
10	ancillary studies		participant data and biological specimens in ancillary	
11			studies, if applicable	
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16	Confidentiality	#27	How personal information about potential and enrolled	11, 18
17			participants will be collected, shared, and maintained in	
18			order to protect confidentiality before, during, and after	
19			the trial	
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26	Declaration of	#28	Financial and other competing interests for principal	21
27	interests		investigators for the overall trial and each study site	
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32	Data access	#29	Statement of who will have access to the final trial	18
33			dataset, and disclosure of contractual agreements that	
34			limit such access for investigators	
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39	Ancillary and post	#30	Provisions, if any, for ancillary and post-trial care, and for	NA
40	trial care		compensation to those who suffer harm from trial	
41			participation	
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47	Dissemination policy:	#31a	Plans for investigators and sponsor to communicate trial	19-20
48	trial results		results to participants, healthcare professionals, the	
49			public, and other relevant groups (eg, via publication,	
50			reporting in results databases, or other data sharing	
51			arrangements), including any publication restrictions	
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1 Dissemination policy: [#31b](#) Authorship eligibility guidelines and any intended use of
 2 authorship professional writers
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 6 Dissemination policy: [#31c](#) Plans, if any, for granting public access to the full NA
 7 reproducible protocol, participant-level dataset, and statistical code
 8 research
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13 Appendices

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 17 Informed consent [#32](#) Model consent form and other related documentation
 18 materials given to participants and authorised surrogates
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 23 Biological specimens [#33](#) Plans for collection, laboratory evaluation, and storage of
 24 biological specimens for genetic or molecular analysis in
 25 the current trial and for future use in ancillary studies, if
 26 applicable
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 33 None The SPIRIT checklist is distributed under the terms of the Creative Commons Attribution
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BMJ Open

Preschool HABIL-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.

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-041542.R1
Article Type:	Protocol
Date Submitted by the Author:	22-Dec-2020
Complete List of Authors:	<p>Sakzewski, Leanne; The University of Queensland, Queensland Cerebral Palsy and Rehabilitation Research Centre, Child Health Research Centre, Faculty of Medicine</p> <p>Reedman, Sarah; The University of Queensland, Queensland Cerebral Palsy and Rehabilitation Research Centre, Child Health Research Centre, Faculty of Medicine</p> <p>McLeod, Kate; Queensland Children's Hospital, Queensland Paediatric Rehabilitation Service</p> <p>Thorley, Megan; Queensland Children's Hospital, Queensland Paediatric Rehabilitation Service</p> <p>Burgess, Andrea; The University of Queensland, Queensland Cerebral Palsy and Rehabilitation Research Centre, Child Health Research Centre, Faculty of Medicine</p> <p>Trost, Stewart; Queensland University of Technology, Institute of Health and Biomedical Innovation, Centre for Children's Health Research</p> <p>Ahmadi, Matthew; Queensland University of Technology, Institute of Health and Biomedical Innovation, Centre for Children's Health Research</p> <p>Rowell, David; University of Queensland, Faculty of Business, Economics and Law</p> <p>Chatfield, Mark; University of Queensland, Cerebral Palsy and Rehabilitation Research Centre, Child Health Research Centre, Faculty of Medicine</p> <p>Bleyenheuft, Yannick; Université catholique de Louvain, Institute of Neuroscience</p> <p>Boyd, Roslyn; The University of Queensland, Queensland Cerebral Palsy and Rehabilitation Research Centre, Child Health Research Centre, Faculty of Medicine</p>
Primary Subject Heading:	Rehabilitation medicine
Secondary Subject Heading:	Paediatrics
Keywords:	Community child health < PAEDIATRICS, REHABILITATION MEDICINE, Paediatric neurology < NEUROLOGY, Developmental neurology & neurodisability < PAEDIATRICS

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3 **Preschool HABIT-ILE: Study protocol for a randomised controlled**
4 **trial to determine efficacy of intensive rehabilitation compared to**
5 **usual care to improve motor skills of children, aged 2 to 5 years,**
6 **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

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3 Service Human Research Ethics Committee (HREC/19/QCHQ/59444) and The
4 University of Queensland (2020000336/HREC/19/QCHQ/59444).
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8 **Trial registration number:** Australian and New Zealand Clinical Trial Registry
9 (ACTRN126200000719).
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13 **Keywords:** gross motor function, manual ability, hand arm bimanual intensive
14 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 reviews⁴⁻⁶ 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 gait⁴. One model of intervention which integrates both upper and lower limb training was developed for

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3 children with unilateral CP. Hand Arm Bimanual Intensive Training Including Lower
4 Extremity training (HABIT-ILE)⁷⁻⁹ is based on known principles of how to induce
5 neuroplasticity incorporating specific, intensive, repetitive task practice. Studies in
6 basic science with animal models, have demonstrated that early intervention based
7 on motor learning principles at critical periods of development, reverse the
8 secondary impact of inflammation post brain injury on neuroplastic processes such
9 as axonal growth, synaptogenesis, myelination and neurogenesis¹⁰⁻¹². To date, two
10 small trials of HABIT-ILE have been conducted, one with school aged children with
11 unilateral CP (n=24)⁸ and one for those with bilateral CP (n=20).⁷ In children with
12 bilateral CP, aged 6 to 15 years, there was a strong effect of HABIT-ILE to improve
13 manual ability (1.6 logit increase on the ABILHAND-Kids), gross motor function (7
14 point increase on the Gross Motor Function Measure) and self-care (8 point increase
15 on the Pediatric Evaluation of Disability Inventory Computer Adapted Test: PEDI-
16 CAT).⁷ A recent systematic review graded HABIT-ILE as a “yellow, probably do it”
17 intervention, as results were promising, but require additional research to increase
18 confidence in the estimate of treatment effect.⁴ We are currently conducting a large
19 clinical trial of HABIT-ILE for school aged children with bilateral CP to confirm and
20 increase certainty in these results.¹³
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36 To date, there remains a major gap in the current evidence for effective interventions
37 for younger children (2-5yrs) with bilateral CP.¹⁴ Children with CP reach 90% of their
38 gross motor/movement potential by 5 years of age or younger, making the first 5
39 years of life a vital window of opportunity to maximize function.¹⁵ In addition, this
40 younger age group is less likely to have secondary complications such as muscle
41 contractures, therefore the magnitude of outcomes possible could be larger than in
42 older children. The current HABIT-ILE dosing schedule for school-aged children with
43 bilateral CP (6.5 hrs/day for 10 days¹³ or 6.5 hours for 13 days⁷) is not feasible to
44 deliver to younger children. Younger children often continue to require a nap time,
45 and are unlikely able to tolerate 6.5 hrs per day of therapy without significant fatigue,
46 therefore a reduced dosing protocol needs to be considered. Content of therapy will
47 differ as games will need to be carefully selected to be age appropriate to engage
48 children and drive self-initiated mobility and bimanual hand use. An adapted dosing
49 schedule and structure of HABIT-ILE needs to be urgently developed and evaluated
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3 for this younger age group, to capitalize on harnessing use-dependent
4 neuroplasticity and maximising motor function.
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8 This pragmatic randomised controlled trial (RCT), Preschool HABIT-ILE will compare
9 this intensive motor training approach to usual care in preschool aged children with
10 bilateral CP (2 to 5 years) at a lower dosing schedule (50 hours) than the original
11 HABIT-ILE studies.^{8 13} This lower dose was selected as it has been shown to be
12 acceptable, feasible and effective with a younger age group children¹⁶ and will be
13 augmented with a structured and written home program¹⁷ to support families to carry
14 out practice within their own context.
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22 **AIMS AND HYPOTHESES**

23 **Broad Aim**

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

55 For preschool aged children with bilateral CP, Preschool HABIT-ILE for a duration of
56 50 hours, will be more effective than usual care to improve:
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[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 COPM²¹;

[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 CP²⁶;

[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;

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

9 **Study Design**

10 This study is a pragmatic RCT in 60 preschool aged children with bilateral CP, which
11 aims to evaluate the effects of Preschool HABIL-ILE (4 hrs/day for 10 days + 10 hrs
12 home practice =total 50 hrs) compared to usual care. The study design has been
13 informed by CONSORT Guidelines²⁷ (see Figure 1).
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18 **Recruitment**

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

41 To be eligible for inclusion, participants must be:

- 42 (a) diagnosed with bilateral CP (diplegia/triplegia/quadruplegia: all motor types), and
43 classified in GMFCS levels II to IV and Manual Abilities Classification System
44 (MACS) / mini-MACS levels I-III;
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46 (b) aged 2 to 5 years;
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48 (c) able to grasp light objects and lift most impaired arm ≥ 15 cm above a table
49 surface;
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51 (d) able to understand and follow instructions in order to complete testing and
52 intervention.
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57 *Exclusion Criteria*

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

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

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

49 The Preschool HABIT-ILE and control interventions are summarised according to the
50 Template for Intervention Description and Replication (TIDieR) Checklist³² in Table
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54 **Preschool HABIT-ILE** is a motor learning approach that simultaneously addresses
55 coordination of the upper and lower limbs.⁹ Key elements of Preschool HABIT-ILE:
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3 *Dose:* 40 hours of therapy achieved through a 2-week intensive group-delivered
4 model for 4 hrs/day over 10 days (Monday to Friday) in addition to a home program
5 for generalization of learning. Home program dose will aim to achieve a further 10
6 hours over the two week intervention period for a total dose of preschool HABIT-ILE
7 of 50 hours.
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11 *Intensity:* The level of intensity will be low to vigorous and will vary across the
12 intervention session. Children will be wearing Polar OH1 Optical Heart Rate monitors
13 during the intervention sessions which will be used in combination with
14 accelerometry to assess intensity of physical activity.
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19 *Mode:* Groups of 4-6 children (1:1 or 2:1 therapist: child ratio according to ability).
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21 *Content and tailoring:* The intervention will be based on the child's motor abilities
22 (determined at baseline), age, interests and caregiver-identified functional goals.
23 Tasks/activities will be made incrementally more challenging. Practice will be
24 embedded in play, using part and whole task practice with high repetition including (i)
25 table top fine motor play-based activities; (ii) activities of daily living when
26 sitting/standing/walking; and (iii) gross motor play. Lower extremity motor abilities
27 and postural control will be progressed from lying to sitting on the floor and then to
28 sitting on a small bench. Transitions will also be progressed from floor-to-sitting-to-
29 standing.
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37 *Intervention providers:* Physiotherapists and occupational therapists, who have
38 completed standardized training and are experienced in delivering HABIT-ILE with
39 older children will form the supervisory team overseeing delivery of Preschool
40 HABIT-ILE. A speech pathologist will consult with the team if children have specific
41 communication (receptive and/or expressive) or feeding difficulties. For 30 minutes,
42 at the conclusion of each session, the child's treating therapy team will meet
43 individually with the child's parent/caregiver/s (one-on one) and discuss the daily
44 program and make suggestions about activities that could be practised at home.
45 These will be detailed on a written Home Program and Practice Log completed by
46 the caregiver. The Home Program activities will be reviewed daily by the child's
47 treating therapy team in collaboration with the child's caregiver and updated as
48 appropriate. Parents will be able to take short videos/photos of home practice
49 activities on their smart phone if they wish to serve as a visual reminder for use at
50 home. In addition, a Therapist Daily Activity Log will be completed by the therapy
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3 team. The Therapist Daily Activity Log is a daily record detailing each activity
4 undertaken by the child. It includes the duration and type of activity (types), position
5 (positions), and number of repetitions or successes (for timed tasks) to assess or
6 monitor participant adherence to the intervention. Furthermore, in combination with
7 videotape (detailed below), logs will act as ground-truth for sensor data in order to
8 assess accuracy and validity of activity classification.
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14 *Location:* Assessments will be conducted at the Centre for Children's Health
15 Research and Queensland Children's Hospital. The intervention will be conducted at
16 the Queensland Paediatric Rehabilitation Service at the Queensland Children's
17 Hospital, South Brisbane, Australia.
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21 Following completion of the HABIT-ILE program, children will return to their usual
22 care therapies.
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25 **Usual Care:** The control group will receive usual care over the six month control
26 period which will vary from weekly to monthly therapy. We expect that the majority of
27 children will be accessing usual care occupational therapy and physiotherapy at an
28 average of one session per week, funded through the National Disability Insurance
29 Scheme. Intervention approaches will be varied and may include
30 neurodevelopmental therapy, developmental therapy, or motor learning-based
31 approaches. Some children may receive alternative "intensive" models of therapy as
32 part of usual care. Families of children in each group will keep a log of usual care
33 therapy including, frequency, duration, mode and content.
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41 **Adverse events and safety**

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43 Any minor or major adverse event associated with Preschool HABIT-ILE will be
44 screened on a daily basis by the treating therapist and will inform the Study
45 Coordinator and Chief Investigators (except major adverse events or those requiring
46 medical treatment, which must be reported as soon as possible, and within 24
47 hours). Minor adverse events include:
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- 50 • Near miss accidents (such as falling off a tricycle or falling heavily in a game)
- 51 • Sore muscles, bruises, other minor injuries not requiring medical treatment
- 52 • Feeling upset, guilty, or sad or fatigued

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57 Major adverse events include:
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- 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).

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

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8 All group intervention sessions will be videotaped and a random selection viewed for
9 fidelity adherence and competence criteria.
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11 **Screening and descriptive measures**

12 All participants will be classified using the:

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

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31 Two qualified, experienced occupational therapists and/or physiotherapists will
32 perform classification at the baseline appointment and will achieve consensus by
33 discussion.
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36 Demographic Questionnaire: A study specific demographic questionnaire will collect
37 information on the child's age, gender, co-morbidities, socio-economic status, family
38 structure and supports, family income and current involvement in rehabilitation
39 programs.
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3 Previous medical history and assessments: Information and copies of Structural
4 neuroimaging (sMRI at 1.5T or 3T) and history of early intervention (e.g. cooling,
5 magnesium sulphate) will be retrieved from the child's medical records. Any sMRI
6 will be retrieved and analysed using automated pipeline³⁹ and semi-quantitative
7 scale of brain lesion severity.^{40 41}
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11 **Primary outcomes**

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

- 23 1. *Gross Motor Function:* Gross Motor Function Measure-66¹⁸ (GMFM-66) is a
24 criterion referenced observation measure developed using Rasch modelling to
25 measure gross motor function of children with CP.¹⁸
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- 27 2. *Bimanual Hand Performance:* Both Hands Assessment¹⁹ (BoHA) measures how
28 children with bilateral CP use their hands together in bimanual activities. Rasch
29 measurement modelling showed strong evidence of internal construct validity, with
30 two separate item difficulty hierarchies for children with: (a) symmetric upper limb
31 use; (b) asymmetric upper limb use.¹⁹ The test uses a selection of toys to elicit
32 bimanual hand use in a structured play session. The BoHA takes 15 to 25 minutes
33 to complete. The BoHA is the only available observational measure of bimanual
34 performance validated for children with bilateral CP, MACS Levels I-III.
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- 36 3. *Self-care, mobility, and social/cognitive functioning:* Pediatric Evaluation of
37 Disability Inventory Computerised Assessment Test (PEDI-CAT): The PEDI-CAT²⁰
38 is a Rasch analysed parent completed questionnaire which measures ability in
39 three functional domains of daily activities (self-care), mobility, and
40 social/cognitive and one domain for responsibility (amount of assistance provided
41 by caregivers to their child to complete complex daily tasks) using normative
42 standard scores and scaled scores with good validity, reliability, and
43 standardisation with typically developing children.^{20 44} The “speedy” version will be
44 used in order to minimise participant assessment burden.
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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 HABIL-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

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

11 A within trial economic evaluation will be conducted to estimate the costs and
12 outcomes of the Preschool HABIT-ILE therapy program. Resource utilization (staff
13 time, equipment and facility use) associated with the delivery of the program will be
14 collected alongside the RCT. Health care utilization will be assessed using a
15 resource use questionnaire previously used in CP child and HABIT-ILE studies.^{13 49}
16 Utility will be derived from the CHU-9D²⁵, a generic child quality of life measure
17 designed specifically for economic evaluation and which has been validated in an
18 Australian population.⁵⁰ Incremental Cost Effectiveness Ratios (ICERs) will be
19 estimated and where appropriate sensitivity analyses undertaken as in previous
20 RCTs by our group.⁵¹
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29 **Ethics and dissemination**

30 Full ethical approval has been granted by the Children's Health Queensland Hospital
31 and Health Service Human Research Ethics Committee (HREC/19/QCHQ/59444),
32 the Medical Research Ethics Committee of The University of Queensland
33 (2020000336/HREC/19/QCHQ/59444). Participant information and consent forms
34 will be provided to all participants and their caregivers prior to entering the study. Full
35 written and informed consent will be obtained from all caregivers of children
36 participating in the trial. The trial has been registered with the Australian and New
37 Zealand Clinical Trial Registry (ACTRN126200000719p). This protocol is reported
38 according to the Standard Protocol Items: Recommendations for Intervention Trials
39 statement (SPIRIT)⁵² and Template for Intervention Description and Replication
40 Checklist (TIDieR).³²
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49 Findings will be disseminated via peer reviewed publication of study results,
50 newsletter feedback to consumers and presentation at key national and international
51 conferences. The authors will plan a knowledge translation pathway if the
52 intervention proves effective in improving motor abilities of preschool aged children
53 with bilateral CP.
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58 **Public/Patient Involvement Statement**

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

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16 Young children with CP reach 90% of their gross motor/movement potential by five
17 years or younger.¹⁵ Sixty percent of children with CP have a bilateral presentation of
18 movement difficulties, yet there is limited evidence for effective interventions to
19 improve their gross motor and manual abilities⁵³. Building on a previous small
20 study⁴⁹ and our current HABIT-ILE Australia project¹³, we aim to test the efficacy of
21 an adapted protocol for younger children aged 2 to 5 years with bilateral CP to
22 improve motor outcomes. One potential limitation of the study is that therapy
23 students under the supervision of trained therapists will be primarily delivering the
24 Preschool HABIT-ILE intervention. As we have done in the larger HABIT-ILE
25 Australia study, we will account for this by providing one day of standardized training
26 for all interventionists, daily debriefing meetings at the end of each day, and ongoing
27 daily feedback from supervising therapists. Secondly, the dose being tested (50
28 hours) was a pragmatic choice based on what is likely to be feasible and acceptable
29 in the Australian context. This dose, however, relies on 10 hours of home practice.
30 We will follow evidence-based processes for the development, delivery and support
31 of parents and caregivers in the implementation of home practice.¹⁷ Usual care is
32 highly variable and may not be at an equivalent dose as the intended Preschool
33 HABIT-ILE. It is not possible to standardize usual care given it is delivered by many
34 different service providers under pre-agreed funding packages. We will however,
35 comprehensively record the type and dose of standard care to determine any
36 differences in dosing schedules and content of intervention. Our inclusion of children
37 classified GMFCS II to IV with all motor types aims to ensure that results are
38 generalizable, however if there is a large differential response to the intervention, the
39 study may be underpowered.
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3 The study has a number of strengths. The number of participants to be included has
4 been calculated for the primary clinical outcome and recruitment is feasible.

5 Selected outcome measures have evidence for both validity and reliability in our
6 population of interest. Standardized interventionist training and fidelity monitoring
7 already developed in our HABIT-ILE Australia¹⁰ study will be adapted, in addition to a
8 with-in trial cost-utility analysis will provide vital information to inform the potential
9 translation of this intervention, particularly in Australia under the National Disability
10 Insurance Scheme. It is anticipated that results of this RCT will be disseminated
11 widely through peer reviewed journals and academic conferences.
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20 Figure 1. Participant flow diagram for Preschool HABIT-ILE.
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23 **Trial Status Update**

24 The study was temporarily paused due to COVID-19. Recruitment has commenced
25 in October 2020 and anticipated commencement of the intervention is in March
26 2021. A 12 month no cost extension on the grant funding this project has been
27 provided.
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34 **Acknowledgments**

35 We acknowledge Sarah Goodman and Dr Natalie Dos Santos, Study Clinical
36 Research Coordinators and the Queensland Paediatric Rehabilitation Service,
37 Queensland Children's Hospital for their support of the project.
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41 **Competing Interests:** None declared
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48 RPCPHD0092017).
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53 **Author Contributions**

54 LS is the chief investigator together with KM, YB and MT developed the intervention
55 protocol. LS, RB, SR, MT and KM designed, established and achieved funding for
56 this study. LS and SR are responsible for ethics applications and reporting. LS, KM,
57 MT, AB, SR are responsible for recruitment and data collection. LS, SR, MT and KM
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3 are responsible for implementation of the interventionist training and fidelity
4 monitoring. SR, ST, MA developed the protocol for evaluation of physical activity and
5 upper limb movement. LS, KM, MT, SR, AB will take the lead roles on preparation for
6 publication of the clinical outcomes; DR, LS and RB will take lead roles of
7 preparation of health economic publications. MC will provide biostatistical advice and
8 oversight for all analyses and publications. LS and the chief investigators drafted the
9 final version of this manuscript. All authors have contributed to the writing and
10 critical review of the manuscript and have approved the final version. All data from
11 this study will be submitted to peer review journals.
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Table 1: TIDieR checklist³² 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	<p>Rationale: Intense, repetitive, active motor learning induces activity dependent neuroplasticity.</p> <p>Essential elements:</p> <ol style="list-style-type: none"> 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 	<p>Rationale: Usual care is highly variable, and may be based on biomechanical, neurodevelopmental, or motor learning principles.</p> <p>Elements may include:</p> <ol style="list-style-type: none"> 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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For peer review only

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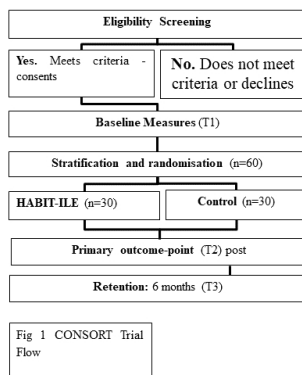


Figure 1. CONSORT Flow Chart

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 SPIRIT reporting 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

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

1	Trial registration	#2a	Trial identifier and registry name. If not yet registered,	4
2			name of intended registry	
3				
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6	Trial registration:	#2b	All items from the World Health Organization Trial	
7			Registration Data Set	
8	data set			
9				
10				
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12	Protocol version	#3	Date and version identifier	footer
13				
14				
15	Funding	#4	Sources and types of financial, material, and other	21
16			support	
17				
18				
19				
20	Roles and	#5a	Names, affiliations, and roles of protocol contributors	1, 21-22
21				
22	responsibilities:			
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24	contributorship			
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28	Roles and	#5b	Name and contact information for the trial sponsor	1
29				
30	responsibilities:			
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32	sponsor contact			
33				
34	information			
35				
36				
37				
38	Roles and	#5c	Role of study sponsor and funders, if any, in study	21-22
39			design; collection, management, analysis, and	
40	responsibilities:		interpretation of data; writing of the report; and the	
41			decision to submit the report for publication, including	
42	sponsor and funder		whether they will have ultimate authority over any of	
43			these activities	
44				
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52	Roles and	#5d	Composition, roles, and responsibilities of the	21-22
53			coordinating centre, steering committee, endpoint	
54	responsibilities:		adjudication committee, data management team, and	
55				
56	committees			
57				
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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

1	Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If	10
2			applicable, eligibility criteria for study centres and	
3			individuals who will perform the interventions (eg,	
4			surgeons, psychotherapists)	
5				
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11	Interventions:	#11a	Interventions for each group with sufficient detail to allow	11-12
12			replication, including how and when they will be	
13	description		administered	
14				
15				
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18				
19	Interventions:	#11b	Criteria for discontinuing or modifying allocated	18
20			interventions for a given trial participant (eg, drug dose	
21	modifications		change in response to harms, participant request, or	
22			improving / worsening disease)	
23				
24				
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28				
29	Interventions:	#11c	Strategies to improve adherence to intervention	13-14
30			protocols, and any procedures for monitoring adherence	
31	adherence		(eg, drug tablet return; laboratory tests)	
32				
33				
34				
35				
36	Interventions:	#11d	Relevant concomitant care and interventions that are	13
37			permitted or prohibited during the trial	
38	concomitant care			
39				
40				
41				
42	Outcomes	#12	Primary, secondary, and other outcomes, including the	15-17
43			specific measurement variable (eg, systolic blood	
44			pressure), analysis metric (eg, change from baseline,	
45			final value, time to event), method of aggregation (eg,	
46			median, proportion), and time point for each outcome.	
47				
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53			Explanation of the clinical relevance of chosen efficacy	
54			and harm outcomes is strongly recommended	
55				
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1	Participant timeline	#13	Time schedule of enrolment, interventions (including any	Consort
2			run-ins and washouts), assessments, and visits for	flow
3			participants. A schematic diagram is highly	chart
4			recommended (see Figure)	
5				
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10				
11	Sample size	#14	Estimated number of participants needed to achieve	18-19
12			study objectives and how it was determined, including	
13			clinical and statistical assumptions supporting any	
14			sample size calculations	
15				
16				
17				
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20				
21	Recruitment	#15	Strategies for achieving adequate participant enrolment	10-11
22			to reach target sample size	
23				
24				
25				
26	Methods:			
27				
28	Assignment of			
29	interventions (for			
30	controlled trials)			
31				
32				
33				
34				
35				
36	Allocation: sequence	#16a	Method of generating the allocation sequence (eg,	10
37	generation		computer-generated random numbers), and list of any	
38			factors for stratification. To reduce predictability of a	
39			random sequence, details of any planned restriction (eg,	
40			blocking) should be provided in a separate document that	
41			is unavailable to those who enrol participants or assign	
42			interventions	
43				
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53	Allocation	#16b	Mechanism of implementing the allocation sequence (eg,	10
54	concealment		central telephone; sequentially numbered, opaque,	
55				
56				
57				
58	mechanism			
59				
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1		sealed envelopes), describing any steps to conceal the	
2		sequence until interventions are assigned	
3			
4			
5			
6	Allocation:	#16c Who will generate the allocation sequence, who will enrol	10
7			
8	implementation	participants, and who will assign participants to	
9		interventions	
10			
11			
12			
13	Blinding (masking)	#17a Who will be blinded after assignment to interventions (eg,	10
14		trial participants, care providers, outcome assessors,	
15		data analysts), and how	
16			
17			
18			
19			
20			
21	Blinding (masking):	#17b If blinded, circumstances under which unblinding is	-
22			
23	emergency	permissible, and procedure for revealing a participant's	
24		allocated intervention during the trial	
25	unblinding		
26			
27			
28			
29	Methods: Data		
30			
31	collection,		
32			
33	management, and		
34			
35	analysis		
36			
37			
38	Data collection plan	#18a Plans for assessment and collection of outcome,	14-17
39		baseline, and other trial data, including any related	
40		processes to promote data quality (eg, duplicate	
41		measurements, training of assessors) and a description	
42		of study instruments (eg, questionnaires, laboratory	
43		tests) along with their reliability and validity, if known.	
44			
45		Reference to where data collection forms can be found, if	
46		not in the protocol	
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1	Data collection plan:	#18b	Plans to promote participant retention and complete	18
2				
3	retention		follow-up, including list of any outcome data to be	
4			collected for participants who discontinue or deviate from	
5			intervention protocols	
6				
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11	Data management	#19	Plans for data entry, coding, security, and storage,	18
12			including any related processes to promote data quality	
13			(eg, double data entry; range checks for data values).	
14			Reference to where details of data management	
15			procedures can be found, if not in the protocol	
16				
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23	Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary	19
24			outcomes. Reference to where other details of the	
25			statistical analysis plan can be found, if not in the	
26			protocol	
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33	Statistics: additional	#20b	Methods for any additional analyses (eg, subgroup and	19
34	analyses		adjusted analyses)	
35				
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37				
38				
39	Statistics: analysis	#20c	Definition of analysis population relating to protocol non-	19
40	population and		adherence (eg, as randomised analysis), and any	
41	missing data		statistical methods to handle missing data (eg, multiple	
42			imputation)	
43				
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47				
48	Methods: Monitoring			
49				
50				
51	Data monitoring:	#21a	Composition of data monitoring committee (DMC);	NA
52	formal committee		summary of its role and reporting structure; statement of	
53			whether it is independent from the sponsor and	
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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

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11	Data monitoring:	#21b	Description of any interim analyses and stopping
12			
13	interim analysis		guidelines, including who will have access to these
14			
15			interim results and make the final decision to terminate
16			
17			the trial
18			
19			
20	Harms	#22	Plans for collecting, assessing, reporting, and managing
21			
22			solicited and spontaneously reported adverse events and
23			
24			other unintended effects of trial interventions or trial
25			
26			conduct
27			
28			
29			
30	Auditing	#23	Frequency and procedures for auditing trial conduct, if
31			
32			any, and whether the process will be independent from
33			
34			investigators and the sponsor
35			
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37			
38	Ethics and		
39			
40	dissemination		
41			
42			
43	Research ethics	#24	Plans for seeking research ethics committee /
44			
45	approval		institutional review board (REC / IRB) approval
46			
47			
48	Protocol	#25	Plans for communicating important protocol modifications
49			
50	amendments		(eg, changes to eligibility criteria, outcomes, analyses) to
51			
52			relevant parties (eg, investigators, REC / IRBs, trial
53			
54			participants, trial registries, journals, regulators)
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1	Consent or assent	#26a	Who will obtain informed consent or assent from potential	19-20
2			trial participants or authorised surrogates, and how (see	
3			Item 32)	
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9	Consent or assent:	#26b	Additional consent provisions for collection and use of	NA
10	ancillary studies		participant data and biological specimens in ancillary	
11			studies, if applicable	
12				
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15				
16	Confidentiality	#27	How personal information about potential and enrolled	11, 18
17			participants will be collected, shared, and maintained in	
18			order to protect confidentiality before, during, and after	
19			the trial	
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26	Declaration of	#28	Financial and other competing interests for principal	21
27	interests		investigators for the overall trial and each study site	
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32	Data access	#29	Statement of who will have access to the final trial	18
33			dataset, and disclosure of contractual agreements that	
34			limit such access for investigators	
35				
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39	Ancillary and post	#30	Provisions, if any, for ancillary and post-trial care, and for	NA
40	trial care		compensation to those who suffer harm from trial	
41			participation	
42				
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47	Dissemination policy:	#31a	Plans for investigators and sponsor to communicate trial	19-20
48	trial results		results to participants, healthcare professionals, the	
49			public, and other relevant groups (eg, via publication,	
50			reporting in results databases, or other data sharing	
51			arrangements), including any publication restrictions	
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1 Dissemination policy: [#31b](#) Authorship eligibility guidelines and any intended use of
2 authorship professional writers
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6 Dissemination policy: [#31c](#) Plans, if any, for granting public access to the full NA
7 reproducible protocol, participant-level dataset, and statistical code
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11 research
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13 Appendices

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

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33 None The SPIRIT checklist is distributed under the terms of the Creative Commons Attribution
34 License CC-BY-ND 3.0. This checklist can be completed online using <https://www.goodreports.org/>, a
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37 tool made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)
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BMJ Open

Preschool HABIL-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.

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-041542.R2
Article Type:	Protocol
Date Submitted by the Author:	29-Jan-2021
Complete List of Authors:	Sakzewski, Leanne; The University of Queensland Faculty of Medicine, Queensland Cerebral Palsy and Rehabilitation Research Centre, Child Health Research Centre Reedman, Sarah; The University of Queensland Faculty of Medicine, Queensland Cerebral Palsy and Rehabilitation Research Centre, Child Health Research Centre McLeod, Kate; Queensland Children's Hospital, Queensland Paediatric Rehabilitation Service Thorley, Megan; Queensland Children's Hospital, Queensland Paediatric Rehabilitation Service Burgess, Andrea; The University of Queensland Faculty of Medicine, Trost, Stewart; Queensland University of Technology, Institute of Health and Biomedical Innovation, Centre for Children's Health Research Ahmadi, Matthew; Queensland University of Technology, Institute of Health and Biomedical Innovation, Centre for Children's Health Research Rowell, David; The University of Queensland, Faculty of Business, Economics and Law Chatfield, Mark; The University of Queensland Faculty of Medicine, Cerebral Palsy and Rehabilitation Research Centre, Child Health Research Centre Bleyenheuft, Yannick; Université catholique de Louvain, Institute of Neuroscience Boyd, Roslyn; The University of Queensland Faculty of Medicine, Queensland Cerebral Palsy and Rehabilitation Research Centre, Child Health Research Centre
Primary Subject Heading:	Rehabilitation medicine
Secondary Subject Heading:	Paediatrics
Keywords:	Community child health < PAEDIATRICS, REHABILITATION MEDICINE, Paediatric neurology < NEUROLOGY, Developmental neurology & neurodisability < PAEDIATRICS

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3 **Preschool HABIL-ILE: Study protocol for a randomised controlled**
4 **trial to determine efficacy of intensive rehabilitation compared to**
5 **usual care to improve motor skills of children, aged 2 to 5 years,**
6 **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

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3 Service Human Research Ethics Committee (HREC/19/QCHQ/59444) and The
4 University of Queensland (2020000336/HREC/19/QCHQ/59444).
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8 **Trial registration number:** Australian and New Zealand Clinical Trial Registry
9 (ACTRN126200000719).
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12

13 **Keywords:** gross motor function, manual ability, hand arm bimanual intensive
14 training including lower extremity, pre-school age.
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18 **Word count: 5372**
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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 reviews⁴⁻⁶ 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 gait⁴. One model of intervention which integrates both upper and lower limb training was developed for

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3 children with unilateral CP. Hand Arm Bimanual Intensive Training Including Lower
4 Extremity training (HABIT-ILE)⁷⁻⁹ is based on known principles of how to induce
5 neuroplasticity incorporating specific, intensive, repetitive task practice. Studies in
6 basic science with animal models, have demonstrated that early intervention based
7 on motor learning principles at critical periods of development, reverse the
8 secondary impact of inflammation post brain injury on neuroplastic processes such
9 as axonal growth, synaptogenesis, myelination and neurogenesis¹⁰⁻¹². To date, two
10 small trials of HABIT-ILE have been conducted, one with school aged children with
11 unilateral CP (n=24)⁸ and one for those with bilateral CP (n=20).⁷ In children with
12 bilateral CP, aged 6 to 15 years, there was a strong effect of HABIT-ILE to improve
13 manual ability (1.6 logit increase on the ABILHAND-Kids), gross motor function (7
14 point increase on the Gross Motor Function Measure) and self-care (8 point increase
15 on the Pediatric Evaluation of Disability Inventory Computer Adapted Test: PEDI-
16 CAT).⁷ A recent systematic review graded HABIT-ILE as a “yellow, probably do it”
17 intervention, as results were promising, but require additional research to increase
18 confidence in the estimate of treatment effect.⁴ We are currently conducting a large
19 clinical trial of HABIT-ILE for school aged children with bilateral CP to confirm and
20 increase certainty in these results.¹³
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36 To date, there remains a major gap in the current evidence for effective interventions
37 for younger children (2-5yrs) with bilateral CP.¹⁴ Children with CP reach 90% of their
38 gross motor/movement potential by 5 years of age or younger, making the first 5
39 years of life a vital window of opportunity to maximize function.¹⁵ In addition, this
40 younger age group is less likely to have secondary complications such as muscle
41 contractures, therefore the magnitude of outcomes possible could be larger than in
42 older children. The current HABIT-ILE dosing schedule for school-aged children with
43 bilateral CP (6.5 hrs/day for 10 days¹³ or 6.5 hours for 13 days⁷) is not feasible to
44 deliver to younger children. Younger children often continue to require a nap time,
45 and are unlikely able to tolerate 6.5 hrs per day of therapy without significant fatigue,
46 therefore a reduced dosing protocol needs to be considered. Content of therapy will
47 differ as games will need to be carefully selected to be age appropriate to engage
48 children and drive self-initiated mobility and bimanual hand use. An adapted dosing
49 schedule and structure of HABIT-ILE needs to be urgently developed and evaluated
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3 for this younger age group, to capitalize on harnessing use-dependent
4 neuroplasticity and maximising motor function.
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8 This pragmatic randomised controlled trial (RCT), Preschool HABIT-ILE will compare
9 this intensive motor training approach to usual care in preschool aged children with
10 bilateral CP (2 to 5 years) at a lower dosing schedule (50 hours) than the original
11 HABIT-ILE studies.^{8 13} This lower dose was selected as it has been shown to be
12 acceptable, feasible and effective with a younger age group children¹⁶ and will be
13 augmented with a structured and written home program¹⁷ to support families to carry
14 out practice within their own context.
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22 **AIMS AND HYPOTHESES**

23 **Broad Aim**

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

55 For preschool aged children with bilateral CP, Preschool HABIT-ILE for a duration of
56 50 hours, will be more effective than usual care to improve:
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[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 COPM²¹;

[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 CP²⁶;

[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;

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

9 **Study Design**

10 This study is a pragmatic RCT in 60 preschool aged children with bilateral CP, which
11 aims to evaluate the effects of Preschool HABIL-ILE (4 hrs/day for 10 days + 10 hrs
12 home practice =total 50 hrs) compared to usual care. The study design has been
13 informed by CONSORT Guidelines²⁷ (see Figure 1).
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18 **Recruitment**

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

41 To be eligible for inclusion, participants must be:

- 42 (a) diagnosed with bilateral CP (diplegia/triplegia/quadruplegia: all motor types), and
43 classified in GMFCS levels II to IV and Manual Abilities Classification System
44 (MACS) / mini-MACS levels I-III;
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46 (b) aged 2 to 5 years;
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48 (c) able to grasp light objects and lift most impaired arm ≥ 15 cm above a table
49 surface;
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51 (d) able to understand and follow instructions in order to complete testing and
52 intervention.
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57 *Exclusion Criteria*

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

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

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

49 The Preschool HABIT-ILE and control interventions are summarised according to the
50 Template for Intervention Description and Replication (TIDieR) Checklist³² in Table
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54 **Preschool HABIT-ILE** is a motor learning approach that simultaneously addresses
55 coordination of the upper and lower limbs.⁹ Key elements of Preschool HABIT-ILE:
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3 *Dose:* 40 hours of therapy achieved through a 2-week intensive group-delivered
4 model for 4 hrs/day over 10 days (Monday to Friday) in addition to a home program
5 for generalization of learning. Home program dose will aim to achieve a further 10
6 hours over the two week intervention period for a total dose of preschool HABIT-ILE
7 of 50 hours.
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11 *Intensity:* The level of intensity will be low to vigorous and will vary across the
12 intervention session. Children will be wearing Polar OH1 Optical Heart Rate monitors
13 during the intervention sessions which will be used in combination with
14 accelerometry to assess intensity of physical activity.
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19 *Mode:* Groups of 4-6 children (1:1 or 2:1 therapist: child ratio according to ability).
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21 *Content and tailoring:* The intervention will be based on the child's motor abilities
22 (determined at baseline), age, interests and caregiver-identified functional goals.
23 Tasks/activities will be made incrementally more challenging. Practice will be
24 embedded in play, using part and whole task practice with high repetition including (i)
25 table top fine motor play-based activities; (ii) activities of daily living when
26 sitting/standing/walking; and (iii) gross motor play. Lower extremity motor abilities
27 and postural control will be progressed from lying to sitting on the floor and then to
28 sitting on a small bench. Transitions will also be progressed from floor-to-sitting-to-
29 standing.
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37 *Intervention providers:* Physiotherapists and occupational therapists, who have
38 completed standardized training and are experienced in delivering HABIT-ILE with
39 older children will form the supervisory team overseeing delivery of Preschool
40 HABIT-ILE. A speech pathologist will consult with the team if children have specific
41 communication (receptive and/or expressive) or feeding difficulties. For 30 minutes,
42 at the conclusion of each session, the child's treating therapy team will meet
43 individually with the child's parent/caregiver/s (one-on one) and discuss the daily
44 program and make suggestions about activities that could be practised at home.
45 These will be detailed on a written Home Program and Practice Log completed by
46 the caregiver. The Home Program activities will be reviewed daily by the child's
47 treating therapy team in collaboration with the child's caregiver and updated as
48 appropriate. Parents will be able to take short videos/photos of home practice
49 activities on their smart phone if they wish to serve as a visual reminder for use at
50 home. In addition, a Therapist Daily Activity Log will be completed by the therapy
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3 team. The Therapist Daily Activity Log is a daily record detailing each activity
4 undertaken by the child. It includes the duration and type of activity (types), position
5 (positions), and number of repetitions or successes (for timed tasks) to assess or
6 monitor participant adherence to the intervention. Furthermore, in combination with
7 videotape (detailed below), logs will act as ground-truth for sensor data in order to
8 assess accuracy and validity of activity classification.
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14 *Location:* Assessments will be conducted at the Centre for Children's Health
15 Research and Queensland Children's Hospital. The intervention will be conducted at
16 the Queensland Paediatric Rehabilitation Service at the Queensland Children's
17 Hospital, South Brisbane, Australia.
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21 Following completion of the HABIT-ILE program, children will return to their usual
22 care therapies.
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25 **Usual Care:** The control group will receive usual care over the six month control
26 period which will vary from weekly to monthly therapy. We expect that the majority of
27 children will be accessing usual care occupational therapy and physiotherapy at an
28 average of one session per week, funded through the National Disability Insurance
29 Scheme. Intervention approaches will be varied and may include
30 neurodevelopmental therapy, developmental therapy, or motor learning-based
31 approaches. Some children may receive alternative "intensive" models of therapy as
32 part of usual care. Families of children in each group will keep a log of usual care
33 therapy including, frequency, duration, mode and content.
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41 **Adverse events and safety**

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43 Any minor or major adverse event associated with Preschool HABIT-ILE will be
44 screened on a daily basis by the treating therapist and will inform the Study
45 Coordinator and Chief Investigators (except major adverse events or those requiring
46 medical treatment, which must be reported as soon as possible, and within 24
47 hours). Minor adverse events include:
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- 50 • Near miss accidents (such as falling off a tricycle or falling heavily in a game)
- 51 • Sore muscles, bruises, other minor injuries not requiring medical treatment
- 52 • Feeling upset, guilty, or sad or fatigued

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57 Major adverse events include:
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- 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

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

- 5 • Intervention manual, related publications.

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

13 Fidelity monitoring

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16 Video footage will be taken for each participating child of the training and progress of
17 tasks towards goal attainment every second day during each HABIT-ILE camp.

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19 Video footage will be reviewed by the HABIT-ILE developer (YB), with regular
20 meetings scheduled throughout each camp to provide feedback on the intensity of
21 delivery, and ongoing support and recommendations for treating therapists.

22 **Screening and descriptive measures**

23 All participants will be classified using the:

- 24 1. Mini-Manual Abilities Classification System (Mini-MACS): The Mini-MACS will
25 classify the child's ability to hand objects in daily activities on a 5-level ordinal
26 scale. The Mini-MACS was developed for children aged 1 to 4 years and has
27 excellent inter-rater reliability (ICC=0.97 between therapists; 0.90 between
28 parents and therapists).³³ The MACS will be used for children over 4 years of
29 age.³⁴
- 30 2. Gross Motor Function Classification System Expanded and Revised
31 (GMFCS): The GMFCS classifies the child's ability to carry out self-generated
32 movements related to sitting and walking on a 5-level ordinal scale.³⁵ The
33 GMFCS has established construct validity, and good inter-rater reliability
34 between therapists.³⁶
- 35 3. Communication Function Classification System (CFCS): The CFCS will be
36 used to classify children's everyday performance of communicating using all
37 methods (e.g. speech, gestures, eye gaze, augmentative and alternative
38 communication) on a five-level ordinal scale.³⁷ There is evidence of content
39 validity, good test re-test reliability, good interrater reliability (0.66) between
40 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 pipeline³⁹ 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-66¹⁸ (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 Assessment¹⁹ (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-CAT²⁰

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

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15 4. *Performance and satisfaction with occupational performance goals*: The Canadian
16 Occupational Performance Measure (COPM)²¹ will be used to measure
17 performance of and satisfaction with parent/caregiver defined self-care, leisure or
18 productivity goals. Test retest reliability is high (ICC 0.76-0.89) and the COPM is
19 responsive to change.²¹ Parents/caregivers will set up to three occupational
20 performance goals. Perceived performance of an individualized goal and
21 satisfaction with performance is rated on a 1-10 scale with higher scores reflecting
22 higher perceived performance and satisfaction.
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25 5. *Global performance in daily activities*: The ACTIVLIM-CP is a Rasch analysed
26 parent completed questionnaire covering a range of daily activities either involving
27 the arms or legs, or both. The questionnaire comprises 43 items on a
28 unidimensional scale, with high reliability (R=0.98) and reproducibility (R=0.97).
29 The questionnaire is suitable for use with children aged 2 to 18 years.²²
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37 6. *Range of executive function*: Behavior Rating Inventory of Executive Function®—
38 Preschool Version (BRIEF-P) measures multiple aspects of executive functioning;
39 scales include Inhibit, Shift, Emotional Control, Working Memory, and
40 Plan/Organize. BRIEF-P is useful in assessing preschool-aged children (aged 2 to
41 5 years 11 months) with acquired neurological, and developmental conditions.²³ A
42 single rating form allows parents to rate a child’s executive functions within the
43 context of his or her everyday environments. BRIEF-P Demonstrates high internal
44 consistency reliability (0.80-0.95 for the parent sample and moderate test-retest
45 reliability (0.78-0.90).²³
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53 7. *Objectively measured physical activity and upper limb movement*: The ActiGraph
54 GT3X+ is a small (4.6cm x 3.3cm x 1.5cm) light weight (19g) triaxial
55 accelerometer which provides valid assessments of habitual physical activity and
56 bimanual performance in children with CP.^{45 46} During the three assessment
57 timepoints, one ActiGraph GT3X+ will be worn on each wrist, one additional
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3 ActiGraph GT3X+ will be worn on the less-affected thigh, and one Polar OH1
4 Optical HR Monitor will be worn on one upper arm during PDMS-2, BoHA, and
5 GMFM-66 assessments. One week prior to each assessment time point, two
6 ActiGraphs (1 less-affected thigh, 1 less-affected wrist) will also be worn in the
7 participant's usual daily life at home (free living) for 7 days during all waking hours
8 at each time-point to assess habitual physical activity. During this time, parents
9 will complete a log book to record their child's activity and position throughout
10 each day. Throughout the 10 day HABIT-ILE intervention, children will wear one
11 ActiGraph GT3X+ on each wrist and on the less-affected thigh, and one Polar
12 OH1 Optical HR Monitor on one upper arm. Data will be processed using count-
13 based methods to objectively quantify change in bimanual performance
14 (asymmetry index) on the BoHA.⁴⁵ The intensity/type of practice during the camp,
15 intensity of free-living habitual physical activity, and time spent ambulatory,
16 transitioning and standing (vs sitting and lying) will be determined using machine
17 learning approaches. HR and inertial data during assessments and camp will
18 enable (1) testing of existing machine-learning models for activity classification,²⁶
19 (2) development of personalized machine-learning models which are
20 hypothesized to be more accurate,²⁶ (3) quantification of the intensity and type of
21 practice during the camp, (4) objective measurement of change in intensity and
22 type of physical activity. Videotapes of therapy sessions and assessments will be
23 used alongside the Therapist Daily Activity Logs as ground-truth for sensor data
24 classification accuracy and validity analysis.

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

53 **Data Management**

54 **Data types:**

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

15 **Data collection:**

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

37 **Management of withdrawals**

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

48 **Sample Size Estimation**

49
50 Based on a difference of 7.5 PDMS-2 Motor Quotients, with an alpha of 5% and 80%
51 power, assuming a standard deviation of 9.2 and buffering for 20% attrition, a
52 sample size of 60 will be required.⁴⁸ We will have 88% power to detect a difference
53 of 5 points or greater on the GMFM-66 (assuming SD=6) and alpha=0.05.

57 **Statistical Analysis**

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

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

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24 A within trial economic evaluation will be conducted to estimate the costs and
25 outcomes of the Preschool HABIT-ILE therapy program. Resource utilization (staff
26 time, equipment and facility use) associated with the delivery of the program will be
27 collected alongside the RCT. Health care utilization will be assessed using a
28 resource use questionnaire previously used in CP child and HABIT-ILE studies.^{13 49}
29 Utility will be derived from the CHU-9D²⁵, a generic child quality of life measure
30 designed specifically for economic evaluation and which has been validated in an
31 Australian population.⁵⁰ Incremental Cost Effectiveness Ratios (ICERs) will be
32 estimated and where appropriate sensitivity analyses undertaken as in previous
33 RCTs by our group.⁵¹
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41 **Ethics and dissemination**

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43 Full ethical approval has been granted by the Children's Health Queensland Hospital
44 and Health Service Human Research Ethics Committee (HREC/19/QCHQ/59444),
45 the Medical Research Ethics Committee of The University of Queensland
46 (2020000336/HREC/19/QCHQ/59444). Participant information and consent forms
47 will be provided to all participants and their caregivers prior to entering the study. Full
48 written and informed consent will be obtained from all caregivers of children
49 participating in the trial. The trial has been registered with the Australian and New
50 Zealand Clinical Trial Registry (ACTRN126200000719p). This protocol is reported
51 according to the Standard Protocol Items: Recommendations for Intervention Trials
52 statement (SPIRIT)⁵² and Template for Intervention Description and Replication
53 Checklist (TIDieR).³²
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3 Findings will be disseminated via peer reviewed publication of study results,
4 newsletter feedback to consumers and presentation at key national and international
5 conferences. The authors will plan a knowledge translation pathway if the
6 intervention proves effective in improving motor abilities of preschool aged children
7 with bilateral CP.
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10 **Public/Patient Involvement Statement**

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

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26 Young children with CP reach 90% of their gross motor/movement potential by five
27 years or younger.¹⁵ Sixty percent of children with CP have a bilateral presentation of
28 movement difficulties, yet there is limited evidence for effective interventions to
29 improve their gross motor and manual abilities⁵³. Building on a previous small
30 study⁴⁹ and our current HABIT-ILE Australia project¹³, we aim to test the efficacy of
31 an adapted protocol for younger children aged 2 to 5 years with bilateral CP to
32 improve motor outcomes. One potential limitation of the study is that therapy
33 students under the supervision of trained therapists will be primarily delivering the
34 Preschool HABIT-ILE intervention. As we have done in the larger HABIT-ILE
35 Australia study, we will account for this by providing one day of standardized training
36 for all interventionists, daily debriefing meetings at the end of each day, and ongoing
37 daily feedback from supervising therapists. Secondly, the dose being tested (50
38 hours) was a pragmatic choice based on what is likely to be feasible and acceptable
39 in the Australian context. This dose, however, relies on 10 hours of home practice.
40 We will follow evidence-based processes for the development, delivery and support
41 of parents and caregivers in the implementation of home practice.¹⁷ Usual care is
42 highly variable and may not be at an equivalent dose as the intended Preschool
43 HABIT-ILE. It is not possible to standardize usual care given it is delivered by many
44 different service providers under pre-agreed funding packages. We will however,
45 comprehensively record the type and dose of standard care to determine any
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3 differences in dosing schedules and content of intervention. Our inclusion of children
4 classified GMFCS II to IV with all motor types aims to ensure that results are
5 generalizable, however if there is a large differential response to the intervention, the
6 study may be underpowered.
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11 The study has a number of strengths. The number of participants to be included has
12 been calculated for the primary clinical outcome and recruitment is feasible.
13 Selected outcome measures have evidence for both validity and reliability in our
14 population of interest. Standardized interventionist training and fidelity monitoring
15 already developed in our HABIT-ILE Australia¹⁰ study will be adapted, in addition to a
16 with-in trial cost-utility analysis will provide vital information to inform the potential
17 translation of this intervention, particularly in Australia under the National Disability
18 Insurance Scheme. It is anticipated that results of this RCT will be disseminated
19 widely through peer reviewed journals and academic conferences.
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29 Figure 1. Participant flow diagram for Preschool HABIT-ILE.
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31 32 **Trial Status Update**

33 The study was temporarily paused due to COVID-19. Recruitment has commenced
34 in October 2020 and anticipated commencement of the intervention is in March
35 2021. A 12 month no cost extension on the grant funding this project has been
36 provided.
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43 **Acknowledgments**

44 We acknowledge Sarah Goodman and Dr Natalie Dos Santos, Study Clinical
45 Research Coordinators and the Queensland Paediatric Rehabilitation Service,
46 Queensland Children's Hospital for their support of the project.
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50 **Competing Interests:** None declared

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55 (AB), Children Hospital Foundation – Lola Hughes Efsthathis Top-Up scholarship (AB,
56 RPCPHD0092017).
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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 checklist³² 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	<p>Rationale: Intense, repetitive, active motor learning induces activity dependent neuroplasticity.</p> <p>Essential elements:</p> <ol style="list-style-type: none"> 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 	<p>Rationale: Usual care is highly variable, and may be based on biomechanical, neurodevelopmental, or motor learning principles.</p> <p>Elements may include:</p> <ol style="list-style-type: none"> 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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For peer review only

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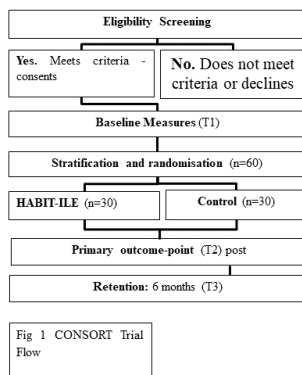


Figure 1. CONSORT Flow Chart

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 SPIRIT reporting 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

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

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

1	Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If	10
2			applicable, eligibility criteria for study centres and	
3			individuals who will perform the interventions (eg,	
4			surgeons, psychotherapists)	
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11	Interventions:	#11a	Interventions for each group with sufficient detail to allow	11-12
12			replication, including how and when they will be	
13	description		administered	
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19	Interventions:	#11b	Criteria for discontinuing or modifying allocated	18
20			interventions for a given trial participant (eg, drug dose	
21	modifications		change in response to harms, participant request, or	
22			improving / worsening disease)	
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29	Interventions:	#11c	Strategies to improve adherence to intervention	13-14
30			protocols, and any procedures for monitoring adherence	
31	adherence		(eg, drug tablet return; laboratory tests)	
32				
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36	Interventions:	#11d	Relevant concomitant care and interventions that are	13
37			permitted or prohibited during the trial	
38	concomitant care			
39				
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42	Outcomes	#12	Primary, secondary, and other outcomes, including the	15-17
43			specific measurement variable (eg, systolic blood	
44			pressure), analysis metric (eg, change from baseline,	
45			final value, time to event), method of aggregation (eg,	
46			median, proportion), and time point for each outcome.	
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53			Explanation of the clinical relevance of chosen efficacy	
54			and harm outcomes is strongly recommended	
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1	Participant timeline	#13	Time schedule of enrolment, interventions (including any	Consort
2			run-ins and washouts), assessments, and visits for	flow
3			participants. A schematic diagram is highly	chart
4			recommended (see Figure)	
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11	Sample size	#14	Estimated number of participants needed to achieve	18-19
12			study objectives and how it was determined, including	
13			clinical and statistical assumptions supporting any	
14			sample size calculations	
15				
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21	Recruitment	#15	Strategies for achieving adequate participant enrolment	10-11
22			to reach target sample size	
23				
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25				
26	Methods:			
27				
28	Assignment of			
29	interventions (for			
30	controlled trials)			
31				
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36	Allocation: sequence	#16a	Method of generating the allocation sequence (eg,	10
37	generation		computer-generated random numbers), and list of any	
38			factors for stratification. To reduce predictability of a	
39			random sequence, details of any planned restriction (eg,	
40			blocking) should be provided in a separate document that	
41			is unavailable to those who enrol participants or assign	
42			interventions	
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53	Allocation	#16b	Mechanism of implementing the allocation sequence (eg,	10
54	concealment		central telephone; sequentially numbered, opaque,	
55				
56				
57				
58	mechanism			
59				
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1		sealed envelopes), describing any steps to conceal the	
2		sequence until interventions are assigned	
3			
4			
5			
6	Allocation:	#16c Who will generate the allocation sequence, who will enrol	10
7			
8	implementation	participants, and who will assign participants to	
9		interventions	
10			
11			
12			
13	Blinding (masking)	#17a Who will be blinded after assignment to interventions (eg,	10
14		trial participants, care providers, outcome assessors,	
15		data analysts), and how	
16			
17			
18			
19			
20			
21	Blinding (masking):	#17b If blinded, circumstances under which unblinding is	-
22			
23	emergency	permissible, and procedure for revealing a participant's	
24		allocated intervention during the trial	
25	unblinding		
26			
27			
28			
29	Methods: Data		
30			
31	collection,		
32			
33	management, and		
34			
35	analysis		
36			
37			
38	Data collection plan	#18a Plans for assessment and collection of outcome,	14-17
39		baseline, and other trial data, including any related	
40		processes to promote data quality (eg, duplicate	
41		measurements, training of assessors) and a description	
42		of study instruments (eg, questionnaires, laboratory	
43		tests) along with their reliability and validity, if known.	
44			
45		Reference to where data collection forms can be found, if	
46		not in the protocol	
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1	Data collection plan:	#18b	Plans to promote participant retention and complete	18
2				
3	retention		follow-up, including list of any outcome data to be	
4			collected for participants who discontinue or deviate from	
5			intervention protocols	
6				
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11	Data management	#19	Plans for data entry, coding, security, and storage,	18
12			including any related processes to promote data quality	
13			(eg, double data entry; range checks for data values).	
14			Reference to where details of data management	
15			procedures can be found, if not in the protocol	
16				
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23	Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary	19
24			outcomes. Reference to where other details of the	
25			statistical analysis plan can be found, if not in the	
26			protocol	
27				
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33	Statistics: additional	#20b	Methods for any additional analyses (eg, subgroup and	19
34	analyses		adjusted analyses)	
35				
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39	Statistics: analysis	#20c	Definition of analysis population relating to protocol non-	19
40	population and		adherence (eg, as randomised analysis), and any	
41	missing data		statistical methods to handle missing data (eg, multiple	
42			imputation)	
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47				
48	Methods: Monitoring			
49				
50				
51	Data monitoring:	#21a	Composition of data monitoring committee (DMC);	NA
52	formal committee		summary of its role and reporting structure; statement of	
53			whether it is independent from the sponsor and	
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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

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11	Data monitoring:	#21b	Description of any interim analyses and stopping
12			
13	interim analysis		guidelines, including who will have access to these
14			
15			interim results and make the final decision to terminate
16			
17			the trial
18			
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20	Harms	#22	Plans for collecting, assessing, reporting, and managing
21			
22			solicited and spontaneously reported adverse events and
23			
24			other unintended effects of trial interventions or trial
25			
26			conduct
27			
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29			
30	Auditing	#23	Frequency and procedures for auditing trial conduct, if
31			
32			any, and whether the process will be independent from
33			
34			investigators and the sponsor
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38	Ethics and		
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40	dissemination		
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43	Research ethics	#24	Plans for seeking research ethics committee /
44			
45	approval		institutional review board (REC / IRB) approval
46			
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48	Protocol	#25	Plans for communicating important protocol modifications
49			
50	amendments		(eg, changes to eligibility criteria, outcomes, analyses) to
51			
52			relevant parties (eg, investigators, REC / IRBs, trial
53			
54			participants, trial registries, journals, regulators)
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1	Consent or assent	#26a	Who will obtain informed consent or assent from potential	19-20
2			trial participants or authorised surrogates, and how (see	
3			Item 32)	
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9	Consent or assent:	#26b	Additional consent provisions for collection and use of	NA
10	ancillary studies		participant data and biological specimens in ancillary	
11			studies, if applicable	
12				
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15				
16	Confidentiality	#27	How personal information about potential and enrolled	11, 18
17			participants will be collected, shared, and maintained in	
18			order to protect confidentiality before, during, and after	
19			the trial	
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26	Declaration of	#28	Financial and other competing interests for principal	21
27	interests		investigators for the overall trial and each study site	
28				
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32	Data access	#29	Statement of who will have access to the final trial	18
33			dataset, and disclosure of contractual agreements that	
34			limit such access for investigators	
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39	Ancillary and post	#30	Provisions, if any, for ancillary and post-trial care, and for	NA
40	trial care		compensation to those who suffer harm from trial	
41			participation	
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47	Dissemination policy:	#31a	Plans for investigators and sponsor to communicate trial	19-20
48	trial results		results to participants, healthcare professionals, the	
49			public, and other relevant groups (eg, via publication,	
50			reporting in results databases, or other data sharing	
51			arrangements), including any publication restrictions	
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1 Dissemination policy: [#31b](#) Authorship eligibility guidelines and any intended use of
2 authorship professional writers
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6 Dissemination policy: [#31c](#) Plans, if any, for granting public access to the full NA
7 reproducible protocol, participant-level dataset, and statistical code
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11 research
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13 Appendices

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17 Informed consent [#32](#) Model consent form and other related documentation
18 materials given to participants and authorised surrogates
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23 Biological specimens [#33](#) Plans for collection, laboratory evaluation, and storage of
24 biological specimens for genetic or molecular analysis in
25 the current trial and for future use in ancillary studies, if
26 applicable
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33 None The SPIRIT checklist is distributed under the terms of the Creative Commons Attribution
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