BMJ Open

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

Leanne Sakzewski ,[1] Sarah Reedman,[1] Kate McLeod,[2] Megan Thorley,[2] Andrea Burgess ,[1] Stewart Trost,[3] Matthew Ahmadi,[4] David Rowell,[5] Mark Chatfield,[1] Yannick Bleyenheuft,[6] Roslyn N Boyd[1]

To cite: Sakzewski L, Reedman S, McLeod K, *et al*. Preschool HABIT-ILE: study protocol for a randomised controlled trial to determine efficacy of intensive rehabilitation compared with usual care to improve motor skills of children, aged 2–5 years, with bilateral cerebral palsy. *BMJ Open* 2021;**11**:e041542. doi:10.1136/bmjopen-2020-041542

► Prepublication history for this paper is available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2020-041542).

Received 11 June 2020
Revised 29 January 2021
Accepted 10 February 2021

For numbered affiliations see end of article.

Correspondence to
Dr Leanne Sakzewski;
l.sakzewski1@uq.edu.au

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 receive Preschool HABIT-ILE or usual care. Preschool HABIT-ILE will be delivered in groups of four to six children, for 3 hours/day for 10 days (total 30 hours). Children receiving Preschool HABIT-ILE be provided a written home programme with the aim of achieving an additional 10 hours of home practice (total dose 40 hours). Outcomes will be assessed at baseline, immediately following intervention and then retention of effects will be tested at 26 weeks. The primary outcome will be the Peabody Developmental Motors Scales–Second Edition to evaluate gross and fine motor skills. Secondary outcomes will be gross motor function (Gross Motor Function Measure-66), bimanual hand performance (Both Hands Assessment), self-care and mobility (Pediatric Evaluation of Disability Inventory-Computer Adapted Test), goal attainment (Canadian Occupational Performance Measure), global performance of daily activities (ACTIVLIM-CP), cognition and adaptive function (Behavior Rating Inventory of Executive Function—Preschool Version), habitual physical activity (ActiGraph GT3X+) and quality of life (Infant Toddler Quality of Life Questionnaire and Child Health Utility Index-9). Analyses will follow standard principles for RCTs using two-group comparisons on all participants on an intention-to-treat basis. Comparisons between groups for primary and secondary outcomes will be conducted using regression models.

Ethics and dissemination Ethics approval has been granted by the Medical Research Ethics Committee Children's Health Queensland Hospital and Health Service Human Research Ethics Committee (HREC/19/

Strengths and limitations of this 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 3-year period, ensuring that the sample size of 60 children across Gross Motor Function Classification System 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 synthesise the costs and benefits of the Preschool Hand Arm Bimanual Intensive Training Including Lower Extremity programme compared with usual care.

QCHQ/59444) and The University of Queensland (2020000336/HREC/19/QCHQ/59444).
Trial registration number ACTRN126200000719.

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 $A5.17 billion, equivalent to $A145 662 per person with CP annually, which includes both the financial costs and also those associated with lost well-being.[2]

There is no cure for CP; it is a life-long condition characterised 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 (eg, smaller brain injuries and greater baseline motor, sensory and learning ability), children may be more likely now than ever to respond positively to motor interventions.[4]

Contemporary proven motor interventions have largely targeted school-aged children with CP and focused on upper and lower extremity motor performance separately.[4 5] To date, significant evidence exists for intensive upper extremity interventions (≈60 hours) to enhance motor performance in children with unilateral CP.[5] A number of systematic reviews[4–6] have consistently identified growing evidence for intensive motor learning based approaches to upper limb rehabilitation for children with unilateral CP (eg, constraint-induced movement therapy, Hand Arm Bimanual Intensive Training) to improve upper limb motor performance. Interventions to target lower compared with upper limb motor performance have generally been less intensive. A recent systematic review identified mobility and treadmill training as effective green light, 'do it' interventions to improve mobility and gait.[4] One model of intervention that integrates both upper and lower limb training was developed for children with unilateral CP. Hand Arm Bimanual Intensive Training Including Lower Extremity training (HABIT-ILE)[7–9] is based on known principles of how to induce neuroplasticity incorporating specific, intensive, repetitive task practice. Studies in basic science with animal models have demonstrated that early intervention based on motor learning principles at critical periods of development reverses the secondary impact of inflammation postbrain injury on neuroplastic processes such as axonal growth, synaptogenesis, myelination and neurogenesis.[10–12] To date, two small trials of HABIT-ILE have been conducted, one with school-aged children with unilateral CP (n=24)[8] and one for those with bilateral CP (n=20).[7] In children with bilateral CP, aged 6–15 years, there was a strong effect of HABIT-ILE to improve manual ability (1.6 logit increase on the ABILHAND-Kids), gross motor function (seven-point increase on the Gross Motor Function Measure) and self-care (eight-point increase on the Pediatric Evaluation of Disability Inventory Computer Adapted Test (PEDI-CAT)).[7] A recent systematic review graded HABIT-ILE as a 'yellow, probably do it' intervention, as results were promising but require additional research to increase confidence in the estimate of treatment effect.[4] We are currently conducting a large clinical trial of HABIT-ILE for school-aged children with bilateral CP to confirm and increase certainty in these results.[13]

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

This pragmatic randomised controlled trial (RCT), Preschool HABIT-ILE, will compare this intensive motor training approach to usual care in preschool-aged children with bilateral CP (2–5 years) at a lower dosing schedule (40 hours) than the original HABIT-ILE studies.[8 13] This lower dose was selected as it has been shown to be acceptable, feasible and effective with a younger age group children[16] and will be augmented with a structured and written home programme[17] to support families to carry out practice within their own context.

AIMS AND HYPOTHESES

Broad aim

This RCT will be conducted in Queensland, Australia, with 60 preschool-aged children (2–5 years) with bilateral CP. This RCT with a pragmatic, single-blind design will determine if Preschool HABIT-ILE is more effective than

usual care to improve gross and fine motor skills (Peabody Developmental Motor Scales – Second Edition (PDMS-2)) immediately postintervention and retention at 26 weeks. Secondary outcomes will test the differential effects of Preschool HABIT-ILE compared with usual care on gross motor function (Gross Motor Function Measure 66 (GMFM-66)), bimanual performance (Both Hands Assessment (BoHA)), self-care and mobility (PEDI-CAT), global performance of daily activities (ACTIVLIM-CP), performance of and satisfaction with parent/caregiver identified occupational performance goals (Canadian Occupational Performance Measure (COPM)), executive functioning (Behavior Rating Inventory of Executive Function Preschool Version (BRIEF-P)), habitual physical activity (7-day free-living accelerometry using ActiGraph GT3X+) and quality of life (Infant Toddler Quality of Life Questionnaire (ITQOL) and the) immediately postintervention and retention at 26 weeks postintervention.

Primary hypothesis

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

1. Gross and fine motor skills total score on the PDMS-2 (difference of 7.5 total motor quotient or equivalent to 0.5 SD) at 3 weeks postbaseline (immediately post intervention) with retention of treatment effects at 6 months postintervention.

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 postintervention and at 26 weeks postintervention to increase:

2. Gross motor function (GMFM-66)[18] motor capacity score.
3. Bimanual hand performance (BoHA).[19]
4. Self-care, mobility, social/cognitive and responsibility (PEDI-CAT).[20]
5. Performance and satisfaction scores on the COPM.[21]
6. Global performance of daily activities (ACTIVLIM-CP).[22]
7. Executive functioning (BRIEF-P).[23]
8. Quality of life (ITQOL and the CHU9 parent proxy).[24 25]
9. Cost-effectiveness $\left(\Delta\$Cost/\Delta CP\ QOL\right)$ 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+):

10. 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.
11. Personalised activity classification machine learning models will have >80% sensitivity and specificity to detect/classify activity type and predict intensity of physical activities in a simulated free-living environment (camp) in preschool-aged children with bilateral CP.[26]
12. Upper limb asymmetry index on the BoHA will decrease in children receiving Preschool HABIT-ILE as compared with control.
13. 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 with control.
14. Children receiving Preschool HABIT-ILE as compared with control will demonstrate a greater proportion of total time in ambulatory, transition and standing activities (vs sitting and lying).

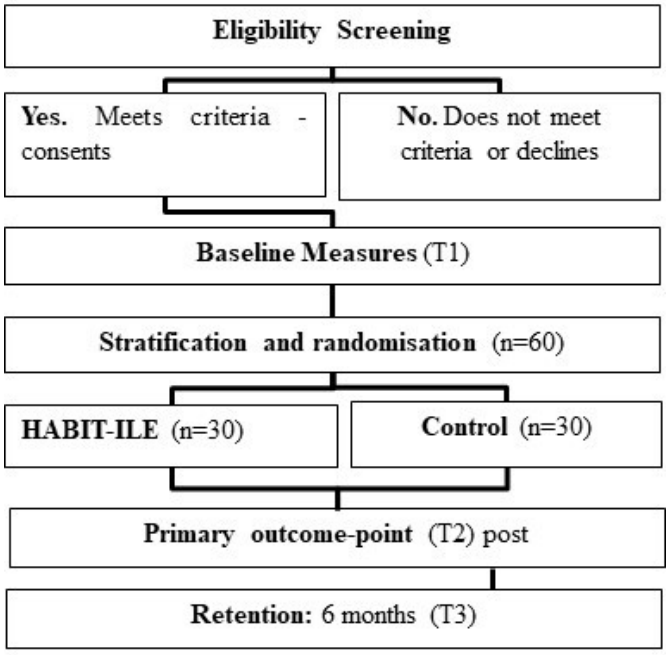

Figure 1 Participant flow diagram for preschool HABIT-ILE. HABIT-ILE, Hand Arm Bimanual Intensive Training Including Lower Extremity training.

METHODS

Study design

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

Recruitment

Sixty preschool-aged children between 2 years corrected age and 5 years 11 months of age at study entry with bilateral CP confirmed by a physician will be recruited. Families with a child meeting eligibility criteria will be invited to join the study through the Queensland Children's Hospital and the Queensland Cerebral Palsy and Rehabilitation Research Centre, The University of Queensland, Brisbane Australia. Recruitment will begin following

ethical and governance approvals. Recruitment will draw on current databases within each organisation and referrals from the clinical service. We do not anticipate problems with our plan to recruit 60 children with bilateral CP as 200 children in Queensland are likely to be eligible (ACPR 2018). The investigators have a strong track record of successfully completing large clinical trials, with all studies achieving recruitment targets.[28–31]

Inclusion criteria

To be eligible for inclusion, participants must be:

1. Diagnosed with bilateral CP (diplegia/triplegia/quadriplegia: all motor types), and classified in GMFCS levels II–IV and Manual Abilities Classification System (MACS)/mini-MACS levels I–III.
2. Aged 2–5 years.
3. Able to grasp light objects and lift most impaired arm ≥15 cm above a table surface.
4. Able to understand and follow instructions in order to complete testing and intervention.

Exclusion criteria

1. Uncontrolled seizures in the previous 6 months (ie, not controlled with medication as this would be a confound and/or exercise risk).
2. Orthopaedic and/or neurological surgery in the 12 months prior to or scheduled during study period (eligible for inclusion if at least 12 months postorthopaedic and/or neurological surgery).
3. A visual impairment interfering with treatment/testing.
4. Unable to actively engage in the assessment process. This will be determined during screening/baseline assessment.

Randomisation

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

Blinding

All outcome assessments at each time point will be administered by experienced physiotherapists (PTs) and occupational therapists (OTs). Objective measures of motor capacity (PDMS-2, BoHA and 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 randomisation. Questionnaire-based measures (ACTIVLIM-CP, ITQOL and CHU9D) will be entered directly into a secure, deidentified 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 randomisation, it will not be possible for participants and their caregivers to be blinded to group allocation.

Study interventions

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

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

Dose

Forty hours of therapy achieved through a 2-week intensive, group-delivered model for 4 hours/day over 10 days (Monday–Friday) in addition to a home programme for generalisation of learning. Home programme dose will aim to achieve a further 10 hours over the 2-week intervention period for a total dose of preschool HABIT-ILE of 50 hours.

Intensity

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

Mode

Groups of four to six children (1:1 or 2:1 therapist:child ratio according to ability).

Content and tailoring

The intervention will be based on the child's motor abilities (determined at baseline), age, interests and caregiver-identified functional goals. Tasks/activities will be made incrementally more challenging. Practice will be embedded in play, using part and whole task practice with high repetition including: (1) table top fine motor play-based activities; (2) activities of daily living when sitting/standing/walking; and (3) gross motor play. Lower extremity motor abilities and postural control will be progressed from lying to sitting on the floor and then to sitting on a small bench. Transitions will also be progressed from floor-to-sitting-to-standing.

Intervention providers

PTs and OTs who have completed standardised training and are experienced in delivering HABIT-ILE with older children will form the supervisory team overseeing delivery of Preschool HABIT-ILE. A speech pathologist will consult with the team if children have specific communication (receptive and/or expressive) or feeding difficulties. For 30 min, at the conclusion of each session, the child's treating therapy team will meet individually with the child's parent/caregiver/s (one on one) and discuss the daily programme and make suggestions about activities that could be practised at home. These will be

Table 1 TIDieR checklist[32] comparison between preschool HABIT-ILE and traditional 'usual care' intervention

Item	Experimental preschool HABIT-ILE	Control 'usual care'
Name	Preschool hand arm bimanual intensive training including lower extremity	Traditional eclectic usual care
Why	Rationale: intense, repetitive, active motor learning induces activity dependent neuroplasticity.	Rationale: usual care is highly variable and may be based on biomechanical, neurodevelopmental or motor learning principles.
	Essential elements:	Elements may include:
	1. Goal directed (goals defined by child/caregiver)	1. Goals defined by either caregiver OR therapist.
	2. Motor training with concurrent challenge for upper and lower limbs and posture.	2. Stretching, splinting and casting.
	3. Shaping	3. Focus on developmental milestones.
	4. Active practice of goals	4. Therapist physically facilitates more typical (normal) movement patterns with children who may be passive recipients.
	5. High repetition and intensity	5. May involve active goal practice using motor learning principles.
		6. Equipment prescription.
Materials	Therapy bench, fit ball to intensely and repeatedly challenge posture; developmentally appropriate 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.	Splints, casts, adaptive equipment to compensate for tasks child cannot perform.
Who	Therapy students (physiotherapy, occupational therapy and 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 and preschool setting.
How much	4 hours/day for 10 weekdays over a 2-week period (total 40 hours)+home programme for 10 hours over 2 weeks for a total dose of 50 hours	Weekly, monthly therapist provided±home programme. 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.

HABIT-ILE, Hand Arm Bimanual Intensive Training Including Lower Extremity training; TIDieR, Template for Intervention Description and Replication.

detailed on a written home programme and practice log completed by the caregiver. The home programme activities will be reviewed daily by the child's treating therapy team in collaboration with the child's caregiver and updated as appropriate. Parents will be able to take short videos/photos of home practice activities on their smartphone if they wish to serve as a visual reminder for use at home. In addition, a therapist daily activity log will be completed by the therapy team. The therapist daily activity log is a daily record detailing each activity undertaken by the child. It includes the duration and type of activity (types), position (positions) and number of repetitions or successes (for timed tasks) to assess or monitor participant adherence to the intervention. Furthermore, in combination with videotape (detailed below), logs will act as ground-truth for sensor data in order to assess accuracy and validity of activity classification.

Location

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

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

Usual care

The control group will receive usual care over the 6-month control period, which will vary from weekly to monthly therapy. We expect that the majority of children will be accessing usual care occupational therapy and physiotherapy at an average of one session per week, funded through the National Disability Insurance Scheme. Intervention approaches will be varied and may include neurodevelopmental therapy, developmental therapy or motor learning-based approaches. Some children may receive alternative 'intensive' models of therapy as part of usual care. Families of children in each group will keep a log of usual care therapy including, frequency, duration, mode and content.

Adverse events and safety

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

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

Major adverse events include:

- Injuries that require medical treatment (such as moderate to 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, PTs and OTs).
- Current basic first aid and cardiac pulmonary resuscitation certificate.
- Evidence of immunisation status (measles, mumps, rubella, pertussis, varicella and hepatitis B).
- A core group of therapists have completed standardised training in HABIT-ILE and have experience conducting a minimum of two HABIT-ILE camps with school aged children. Standardised training was provided to this core group of therapists (a minimum of one OT and one PT) 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 PTs and OTs and undergraduate PT and OT therapy students. It is required that therapists/therapy students possess the following attributes:

- Full registration with the AHPRA (PTs and OTs) OR evidence of enrolment in a relevant undergraduate course.
- Current basic first aid and cardiac pulmonary resuscitation certificate.
- Evidence of immunisation status.

Therapist/student training

Onsite standardised interventionist training developed by LS, SR and YB will be provided to therapists/students by the supervisory team (LS, KM and MT) who will deliver the intervention. This will occur in the week prior to each camp. The 1-day training package will include:

- Intervention manual and related publications.

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

Fidelity monitoring

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

Screening and descriptive measures

All participants will be classified using the:

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

Two qualified, experienced OTs and/or PTs 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, comorbidities, socioeconomic status, family structure and supports, family income and current involvement in rehabilitation programmes.

Previous medical history and assessments

Information and copies of structural neuroimaging (sMRI at 1.5T or 3T) and history of early intervention (eg, cooling, magnesium sulphate) will be retrieved from the child's medical records. Any sMRI will be retrieved and analysed using automated pipeline[39] and semiquantitative scale of brain lesion severity.[40 41]

Primary outcomes

Fine and gross motor skills

The 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: GMFM-66[18] is a criterion referenced observation measure developed using Rasch modelling to measure gross motor function of children with CP.[18]
2. Bimanual hand performance: BoHA[19] 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 and (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 15–25 min 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: PEDI-CAT[20] is a Rasch-analysed parent-completed questionnaire that measures ability in three functional domains of daily activities (self-care), mobility and social/cognitive and one domain for responsibility (amount of assistance provided by caregivers to their child to complete complex daily tasks) using normative standard scores and scaled scores with good validity, reliability and standardisation with typically developing children.[20 44] The 'speedy' version will be used in order to minimise participant assessment burden.
4. Performance and satisfaction with occupational performance goals: The 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 individualised 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 2–18 years.[22]
6. Range of executive function: BRIEF-P measures multiple aspects of executive functioning; scales include inhibit, shift, emotional control, working memory and plan/organise. BRIEF-P is useful in assessing preschool-aged children (aged 2–5 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 (4.6 cm × 3.3cm × 1.5 cm) lightweight (19 g) triaxial accelerometer that 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 (one less-affected thigh, one 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 personalised machine-learning

models that are hypothesised to be more accurate,[26] (3) quantification of the intensity and type of practice during the camp and (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 ITQOL is designed for infants aged 2 months–5 years of age.[24] The ITQOL comprises 97 items, with good evidence for discriminative validity and reliability.[47] The Child Health Utility 9 (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 2–5 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 and ACTIVLIM-CP), one questionnaire measuring cognition and adaptive function (BRIEF-P), three questionnaires assessing their child's quality of life (ITQOL and CHU9) and HRU that will be used for the health economic analysis. All data will be reidentifiable.

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

Health economics

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

ETHICS AND DISSEMINATION

Full ethical approval has been granted by the Children's Health Queensland Hospital and Health Service Human

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

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

Public/patient involvement statement

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

DISCUSSION

Young children with CP reach 90% of their gross motor/movement potential by 5 years or younger.[15] Sixty per cent of children with CP have a bilateral presentation of movement difficulties, yet there is limited evidence for effective interventions to improve their gross motor and manual abilities.[53] Building on a previous small study[49] and our current HABIT-ILE Australia project,[13] we aim to test the efficacy of an adapted protocol for younger children aged 2–5 years with bilateral CP to improve motor outcomes. One potential limitation of the study is that therapy students under the supervision of trained therapists will be primarily delivering the Preschool HABIT-ILE intervention. As we have done in the larger HABIT-ILE Australia study, we will account for this by providing 1 day of standardised training for all interventionists, daily debriefing meetings at the end of each day and ongoing daily feedback from supervising therapists. Second, the dose being tested (50 hours) was a pragmatic choice based on what is likely to be feasible and acceptable in the Australian context. This dose, however, relies on 10 hours of home practice. We will follow evidence-based processes for the development, delivery and support of parents and caregivers in the implementation of home practice.[17] Usual care is highly variable and may not be at an equivalent dose as the intended Preschool HABIT-ILE. It is not possible to standardise usual care given it is delivered by many different service providers under pre-agreed funding packages. We will, however, comprehensively record the type and dose of standard care to determine any differences in dosing schedules and content of intervention. Our inclusion of children classified GMFCS II–IV with all motor types aims to ensure that results are generalisable; however, if there is a large differential response to the intervention, the study may be underpowered.

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

Trial status update

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

Author affiliations
[1]Queensland Cerebral Palsy and Rehabilitation Research Centre, Child Health Research Centre, The University of Queensland Faculty of Medicine, Herston, Queensland, Australia
[2]Queensland Paediatric Rehabilitation Service, Queensland Children's Hospital, South Brisbane, Queensland, Australia
[3]Institute of Health and Biomedical Innovation, Centre for Children's Health Research, Queensland University of Technology, Brisbane, Queensland, Australia
[4]Faculty of Medicine and Health, School of Health Sciences, Charles Perkins Centre, Camperdown, New South Wales, Australia
[5]Faculty of Business, Economics and Law, The University of Queensland, Saint Lucia, Queensland, Australia
[6]Institute of Neuroscience, Université catholique de Louvain, Louvain-la-Neuve, Belgium

Twitter Sarah Reedman @sarah_reedman

Acknowledgements We acknowledge Sarah Goodman and Dr Natalie Dos Santos, Study Clinical Research Coordinators and the Queensland Paediatric Rehabilitation Service, Queensland Children's Hospital, for their support of the project.

Contributors LS is the chief investigator together with KM, YB and MT developed the intervention protocol. LS, RNB, 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 and 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 and MA developed the protocol for evaluation of physical activity and upper limb movement. LS, KM, MT, SR and 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-reviewed journals.

Funding This work is supported by a Ramaciotti Health Investment Grant (2019HIG/043) National Health and Medical Research Council (NHMRC) Career Development Fellowship (LS, 1160694); NHMRC Research Fellowship (RB, 1105038). Australian Government Research Training scholarship (AB) and Children Hospital Foundation – Lola Hughes Efstathis Top-Up scholarship (AB, RPCPHD0092017).

Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iDs
Leanne Sakzewski http://orcid.org/0000-0001-5395-544X
Andrea Burgess http://orcid.org/0000-0001-8697-5156

REFERENCES

1 Galea C, Mcintyre S, Smithers-Sheedy H, *et al*. Cerebral palsy trends in Australia (1995-2009): a population-based observational study. *Dev Med Child Neurol* 2019;61:186–93.
2 Deloitte Access Economics. *The cost of cerebral palsy in Australia in 2018*, 2019.
3 Badawi N, Keogh JM. Causal pathways in cerebral palsy. *J Paediatr Child Health* 2013;49:5–8.
4 Novak I, Morgan C, Fahey M, *et al*. State of the evidence traffic lights 2019: systematic review of interventions for preventing and treating children with cerebral palsy. *Curr Neurol Neurosci Rep* 2020;20:3.
5 Sakzewski L, Ziviani J, Boyd RN. Efficacy of upper limb therapies for unilateral cerebral palsy: a meta-analysis. *Pediatrics* 2014;133:e175–204.
6 Chen Y-P, Pope S, Tyler D, *et al*. Effectiveness of constraint-induced movement therapy on upper-extremity function in children with cerebral palsy: a systematic review and meta-analysis of randomized controlled trials. *Clin Rehabil* 2014;28:939–53.
7 Bleyenheuft Y, Ebner-Karestinos D, Surana B, *et al*. Intensive upper- and lower-extremity training for children with bilateral cerebral palsy: a quasi-randomized trial. *Dev Med Child Neurol* 2017;59:625–33.
8 Bleyenheuft Y, Arnould C, Brandao MB, *et al*. Hand and arm bimanual intensive therapy including lower extremity (HABIT-ILE) in children with unilateral spastic cerebral palsy: a randomized trial. *Neurorehabil Neural Repair* 2015;29:645–57.
9 Bleyenheuft Y, Gordon AM. Hand-arm bimanual intensive therapy including lower extremities (HABIT-ILE) for children with cerebral palsy. *Phys Occup Ther Pediatr* 2014;34:390–403.
10 Martin JH, Chakrabarty S, Friel KM. Harnessing activity-dependent plasticity to repair the damaged corticospinal tract in an animal model of cerebral palsy. *Dev Med Child Neurol* 2011;53:9–13.
11 Friel KM, Williams PTJA, Serradj N, *et al*. Activity-Based therapies for repair of the corticospinal system injured during development. *Front Neurol* 2014;5:229.
12 Martin JH, Friel KM, Salimi I, *et al*. Activity- and use-dependent plasticity of the developing corticospinal system. *Neurosci Biobehav Rev* 2007;31:1125–35.
13 Sakzewski L, Bleyenheuft Y, Boyd RN, *et al*. Protocol for a multisite randomised trial of hand-arm bimanual intensive training including lower extremity training for children with bilateral cerebral palsy: HABIT-ILE Australia. *BMJ Open* 2019;9:e032194.
14 Novak I, McIntyre S, Morgan C, *et al*. A systematic review of interventions for children with cerebral palsy: state of the evidence. *Dev Med Child Neurol* 2013;55:885–910.
15 Palisano RJ, Hanna SE, Rosenbaum PL, *et al*. Validation of a model of gross motor function for children with cerebral palsy. *Phys Ther* 2000;80:974–85.
16 Araneda R, Klöcker A, Ebner-Karestinos D, *et al*. Feasibility and effectiveness of HABIT-ILE in children aged 1 to 4 years with cerebral palsy: a pilot study. *Ann Phys Rehabil Med* 2020:101381.
17 Novak I, Cusick A, Lannin N. Occupational therapy home programs for cerebral palsy: double-blind, randomized, controlled trial. *Pediatrics* 2009;124:e606–14.
18 Russell DJ, Avery LM, Rosenbaum PL, *et al*. Improved scaling of the gross motor function measure for children with cerebral palsy: evidence of reliability and validity. *Phys Ther* 2000;80:873–85.
19 Elvrum A-KG, Zethræus B-M, Vik T, *et al*. Development and validation of the both hands assessment for children with bilateral cerebral palsy. *Phys Occup Ther Pediatr* 2018;38:113–26.
20 Haley SM, Coster WJ, Dumas HM, *et al*. Accuracy and precision of the pediatric evaluation of disability inventory computer-adaptive tests (PEDI-CAT). *Dev Med Child Neurol* 2011;53:1100–6.
21 Law M, Baptiste S, Carswell A. *Canadian occupational performance measure*. 3rd edn. Ottawa,Ontario: CAOT Publications, 1998.
22 Bleyenheuft Y, Paradis J, Renders A, *et al*. ACTIVLIM-CP a new Rasch-built measure of global activity performance for children with cerebral palsy. *Res Dev Disabil* 2017;60:285–94.
23 Gioia G, Espy K, Isquith P. *Behavior Rating Inventory of Executive Function - Preschool Version*. Lutz, FL: Psychological Assessment Resources, 2003.
24 Raat H, Landgraf JM, Oostenbrink R, *et al*. Reliability and validity of the infant and toddler quality of life questionnaire (ITQOL) in a general population and respiratory disease sample. *Qual Life Res* 2007;16:445–60.
25 Stevens K. Valuation of the child health utility 9D index. *Pharmacoeconomics* 2012;30:729–47.
26 Ahmadi M, O'Neil M, Fragala-Pinkham M, *et al*. Machine learning algorithms for activity recognition in ambulant children and adolescents with cerebral palsy. *J Neuroeng Rehabil* 2018;15:105.
27 Schulz KF, Altman DG, Moher D, *et al*. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *PLoS Med* 2010;7:e1000251.
28 Copeland L, Edwards P, Thorley M, *et al*. Botulinum toxin A for nonambulatory children with cerebral palsy: a double blind randomized controlled trial. *J Pediatr* 2014;165:140–6.
29 Sakzewski L, Miller L, Ziviani J, *et al*. Randomized comparison trial of density and context of upper limb intensive group versus individualized occupational therapy for children with unilateral cerebral palsy. *Dev Med Child Neurol* 2015;57:539–47.
30 Sakzewski L, Ziviani J, Abbott DF, *et al*. Randomized trial of constraint-induced movement therapy and bimanual training on activity outcomes for children with congenital hemiplegia. *Dev Med Child Neurol* 2011;53:313–20.
31 Thomas RE, Johnston LM, Sakzewski L, *et al*. Evaluation of group versus individual physiotherapy following lower limb intra-muscular botulinum Toxin-Type a injections for ambulant children with cerebral palsy: a single-blind randomized comparison trial. *Res Dev Disabil* 2016;53-54:267–78.
32 Hoffmann TC, Glasziou PP, Boutron I, *et al*. Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. *BMJ* 2014;348:g1687.
33 Eliasson A-C, Ullenhag A, Wahlström U, *et al*. Mini-MACS: development of the manual ability classification system for children younger than 4 years of age with signs of cerebral palsy. *Dev Med Child Neurol* 2017;59:72–8.
34 Eliasson A-C, Krumlinde-Sundholm L, Rösblad B, *et al*. The manual ability classification system (MACS) for children with cerebral palsy: scale development and evidence of validity and reliability. *Dev Med Child Neurol* 2006;48:549–54.
35 Rosenbaum PL, Palisano RJ, Bartlett DJ, *et al*. Development of the gross motor function classification system for cerebral palsy. *Dev Med Child Neurol* 2008;50:249–53.
36 Palisano RJ, Rosenbaum P, Bartlett D, *et al*. Content validity of the expanded and revised gross motor function classification system. *Dev Med Child Neurol* 2008;50:744–50.
37 Hidecker MJC, Paneth N, Rosenbaum PL, *et al*. Developing and validating the communication function classification system for individuals with cerebral palsy. *Dev Med Child Neurol* 2011;53:704–10.
38 Mutlu A, Kara Özgün Kaya, Livanelioğlu A, *et al*. Agreement between parents and clinicians on the communication function levels and relationship of classification systems of children with cerebral palsy. *Disabil Health J* 2018;11:281–6.
39 Pagnozzi AM, Dowson N, Fiori S, *et al*. Alterations in regional shape on ipsilateral and contralateral cortex contrast in children with unilateral cerebral palsy and are predictive of multiple outcomes. *Hum Brain Mapp* 2016;37:3588–603.

40 Pannek K, Boyd RN, Fiori S, *et al*. Assessment of the structural brain network reveals altered connectivity in children with unilateral cerebral palsy due to periventricular white matter lesions. *Neuroimage Clin* 2014;5:84–92.
41 Fiori S, Cioni G, Klingels K, *et al*. Reliability of a novel, semi-quantitative scale for classification of structural brain magnetic resonance imaging in children with cerebral palsy. *Dev Med Child Neurol* 2014;56:839–45.
42 Folio M, Fewell R. *Peabody developmental motor scales: examiner's manual*. 2nd edn. Austin, Texas: PRO-ED Inc, 2000.
43 Wang H-H, Liao H-F, Hsieh C-L. Reliability, sensitivity to change, and responsiveness of the peabody developmental motor scales-second edition for children with cerebral palsy. *Phys Ther* 2006;86:1351–9.
44 Fragala-Pinkham MA, Miller PE, M Dumas H, *et al*. Development and validation of equations to link pediatric evaluation of disability inventory (PEDI) functional skills scores to PEDI-Computer adaptive test scores for youth with cerebral palsy. *Phys Occup Ther Pediatr* 2020;40:106–20.
45 Beani E, Maselli M, Sicola E, *et al*. Actigraph assessment for measuring upper limb activity in unilateral cerebral palsy. *J Neuroeng Rehabil* 2019;16:30.
46 Braito I, Maselli M, Sgandurra G, *et al*. Assessment of upper limb use in children with typical development and neurodevelopmental disorders by inertial sensors: a systematic review. *J Neuroeng Rehabil* 2018;15:94.
47 Landgraf JM, Vogel I, Oostenbrink R, *et al*. Parent-reported health outcomes in infants/toddlers: measurement properties and clinical validity of the ITQOL-SF47. *Qual Life Res* 2013;22:635–46.
48 Morgan C, Novak I, Dale RC, *et al*. Optimising motor learning in infants at high risk of cerebral palsy: a pilot study. *BMC Pediatr* 2015;15:30.
49 Boyd RN, Jordan R, Pareezer L, *et al*. Australian cerebral palsy child study: protocol of a prospective population based study of motor and brain development of preschool aged children with cerebral palsy. *BMC Neurol* 2013;13:57.
50 Ratcliffe J, Flynn T, Terlich F, *et al*. Developing adolescent-specific health state values for economic evaluation: an application of profile case best-worst scaling to the child health utility 9D. *Pharmacoeconomics* 2012;30:713–27.
51 Comans T, Mihala G, Sakzewski L, *et al*. The cost-effectiveness of a web-based multimodal therapy for unilateral cerebral palsy: the Mitii randomized controlled trial. *Dev Med Child Neurol* 2017;59:756–61.
52 Chan A-W, Tetzlaff JM, Altman DG, *et al*. SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Ann Intern Med* 2013;158:200–7.
53 Plasschaert VFP, Vriezekolk JE, Aarts PBM, *et al*. Interventions to improve upper limb function for children with bilateral cerebral palsy: a systematic review. *Dev Med Child Neurol* 2019;61:899–907.