Protocol for a Multi-site Randomised Trial of Hand Arm Bimanual Intensive Training Including Lower Extremity Training for Children with Bilateral Cerebral Palsy: HABIT-ILE Australia.

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Abstract

Introduction: Children with bilateral cerebral palsy often experience difficulties with posture, gross motor function and manual ability, impacting 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. This study aims to compare HABIT-ILE to usual care in a large randomised controlled trial (RCT) in terms of gross motor function, manual ability, goal attainment, walking endurance, mobility, self-care and quality of life. A within trial cost-utility analysis will be conducted to synthesize costs and benefits of HABIT-ILE compared to usual care.

Methods and analysis: 126 children with bilateral cerebral palsy aged 6-16 years will be recruited across three sites in Australia. Children will be stratified by site and Gross Motor Function Classification and randomised using concealed allocation to either receiving HABIT-ILE immediately or be waitlisted for 26 weeks. HABIT-ILE will be delivered in groups of 8 to 12 children, for 6.5 hrs per day for 10 days (total 65 hrs two weeks). Outcomes will be assessed at baseline, immediately following intervention and then retention of effects will be tested at 26 weeks. Primary outcomes will be the Gross Motor Function Measure and ABILHAND-Kids. Secondary outcomes will be brain structural integrity, walking endurance, bimanual hand performance, self-care, mobility, performance and satisfaction with individualised goals 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/17/QRCH/282) and The University of Queensland (2018000017/HREC/17/QRCH/2820), and The Cerebral Palsy Alliance Ethics Committee (2018_04_01/HREC/17/QRCH/282).

Trial registration number: Australian and New Zealand Clinical Trial Registry (ACTRN12618000164291).

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

Strengths and limitations of the study

- This is a large randomised controlled trial investigating the efficacy of an intensive motor training approach to improve gross motor function and manual ability for children with bilateral cerebral palsy, powered to test both primary and secondary outcomes.
- Potential participants will be recruited from three centres in Australia, ensuring that the sample size will be met.
- Outcomes include gross motor function, manual ability, brain structure and function, self-care, mobility, bimanual performance, quality of life, and self-perceived performance of and satisfaction with individually defined functional goals.
- A fidelity framework includes standardised training of interventionists and fidelity monitoring of each intervention day camp.
- A comprehensive within trial cost-utility analysis will be conducted to synthesize the costs and benefits of the HABIT-ILE program compared to usual care.

INTRODUCTION

Cerebral palsy (CP) is the most common physical disability in childhood[1] with an estimated prevalence of 1.4 in 1000 live births.[2] Six hundred children are newly diagnosed with CP each year, with greater than 35,000 people living with CP in Australia.[3] Over 61% of children with CP have "bilateral" motor involvement, impairing movement on both sides of the body.[1] For some of these children, all four limbs and trunk are affected making both walking and effective upper limb use challenging. These limitations significantly impact their independence and participation in home, school, work and community life.[4] People with CP have poorer health outcomes compared to age matched peers.[5] Increased severity of physical disability is associated with reduced general health, greater pain and discomfort,[5] reduced independence in daily life skills[6] and poorer vocational outcomes.[7] Interventions that reduce the impact of the physical disability and promote independence in daily life skills, inclusion and community participation are essential.

Traditional neurodevelopmental interventions were frequently based on passive movement experiences using passively guided movements (with the aim of normalising movement) as well as passive manual stretching (aimed to improve or maintain range of motion and decrease contractures and spasticity). These have been shown to be ineffective in improving motor outcomes for children with CP.[8-9] Contemporary and proven effective interventions for school-aged children with CP involve child-active task-specific motor training from the motor learning paradigm, such as Constraint Induced Movement Therapy, Bimanual Training and Goal Directed Training.[4] Since these interventions predominantly target upper and lower extremity motor performance separately, the evidence bases are different.[8-9] There have been fewer studies investigating task-specific interventions to target lower compared to upper limb motor performance. A recent systematic review identified the effectiveness of specific gait training in increasing gait speed for children with unilateral and bilateral CP (Effect Size (ES) = 0.92; p=0.01).[10] To date, significant evidence exists for intensive upper extremity interventions (≈60 hours) to enhance upper limb motor performance in children with unilateral CP.[8] A number of systematic reviews and meta-analyses[8-9, 11] have confirmed growing evidence for intensive contemporary motor learning based approaches to upper limb training for school aged children with unilateral CP (e.g. Constraint induced movement therapy,

Hand Arm Bimanual Intensive Training [HABIT]) to improve upper limb motor performance.

Since children with bilateral CP often have both upper and lower limbs involved, "HABIT-ILE" was invented to treat both the upper and lower limbs concurrently. In children with unilateral CP, a randomised control trial (RCT) demonstrated the efficacy of HABIT-ILE for both the upper and lower extremities.[12] Results obtained from concurrent upper and lower extremity training were similar to those obtained by children who received upper extremity training alone.[12] These findings led researchers to test whether HABIT-ILE intervention might be helpful for children with bilateral CP. A recent systematic review of interventions to improve upper limb function in children with bilateral CP, however, found a large variety of different interventions addressing upper limb function but most studies had weak to moderate methodological quality.[13] The strongest evidence was from a small quasi-randomised controlled trial (RCT) of Hand Arm Bimanual Intensive Training Including Lower Extremity (HABIT-ILE) and the authors highlighted the need for further high quality trials.[13] Compared to a waitlist control group, children with bilateral CP who received 84 hours of HABIT-ILE achieved significantly greater gains in manual ability (ABILHAND-Kids n^2=0.32; p<0.001), self-care on the Pediatric Evaluation of Disability Inventory (PEDI; n^2=0.26; p=0.001), gross motor function on the Gross Motor Function Measure 66-item (GMFM-66: n^2=0.33; p<0.001), walking distance on the 6 Minute Walk Test (6MWT: n^2=0.17; p<0.03) and balance on the Pediatric Balance Scale (PBS: n^2=0.28; p<0.002). These promising results indicate that a larger randomized controlled trial (RCT) is warranted to confirm the efficacy of HABIT-ILE on manual ability and gross motor function for children with bilateral CP. This multi-site RCT, HABIT-ILE Australia, will compare this intensive motor training approach to usual care in school aged children with bilateral CP at a lower dose than the original study (65 hours versus 90 hours). This lower dose was selected based on potential acceptability and feasibility within the Australian context.

AIMS AND HYPOTHESES

Broad Aim

This multi-site RCT will be conducted in three Australian states (Queensland, New South Wales, and Western Australia) with 126 school aged children with bilateral

CP. This RCT with a pragmatic, single-blind design will determine if HABIT-ILE is more effective than usual care to improve manual ability (ABILHAND-Kids) and gross motor function (GMFM-66) immediately post intervention and retention at 26 weeks. Secondary outcomes will test the differential effects of HABIT-ILE compared to usual care on neuroplastic changes in brain structural integrity, functional and structural connectivity, walking endurance (6MWT), self-care and mobility (PEDI-CAT), bimanual performance (Both Hands Assessment: BoHA), performance of and satisfaction with individualized occupational performance goals (Canadian Occupational Performance Measure: COPM), and quality of life (CP Quality of Life Questionnaire: CP QOL-Child or CP QOL-Teen) immediately post intervention and retention at 26 weeks after the intervention.

Primary Hypotheses

For children with bilateral CP, HABIT-ILE for a duration of 65 hours will be more effective than a waitlist control group receiving usual care to improve:

[i] manual ability on the ABILHAND-KIDS by a difference of 1.6 logits or greater and;

[ii] gross motor function on the GMFM-66 by a difference of 5 points or greater.

Secondary Hypotheses

For children with bilateral CP, HABIT-ILE for a duration of 65 hours will be more effective than a waitlist control group receiving usual care to increase:

[iii] Brain structural integrity measured using fMRI guided tractography;[14]

[iv] Walking endurance (6MWT);[15]

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

[vi] Self-care and mobility (PEDI-CAT);[17]

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

[viii] Quality of Life (CP QOL-Child or CP QOL-Teen, parent proxy and child report; and the Child Health Utility Index CHU9 parent proxy).[19-20]

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

METHODS

Study Design

This single-blind RCT will compare HABIT-ILE to usual care for school aged children with bilateral CP. Study design has been informed by CONSORT Guidelines (see Figure 1).

Recruitment

One hundred and twenty-six school aged children between 6 and 16 years of age at study entry with bilateral CP will be recruited. Families with a child meeting eligibility criteria will be invited to join the study through our three collaborating sites and associated clinical services (Queensland Children's Hospital, Cerebral Palsy Alliance, and Perth Children's Hospital). Recruitment from three major metropolitan centres will enable the target sample size to be achieved (50 in New South Wales (NSW), 50 in Queensland (QLD) and 26 in Western Australia (WA)).

Recruitment at each site will begin following ethical and governance approvals. Recruitment will draw upon current databases within each organization, referrals from clinical services. Based on population numbers available on the Australian Cerebral Palsy Register (1240 potentially eligible participants) and well-established state-wide clinical networks, recruitment of 126 participants is feasible across the three sites. It is expected that final data collection will occur in July 2020.

Inclusion Criteria

To be eligible for inclusion, participants must be:

(a) diagnosed with bilateral CP (diplegia/triplegia/quadriplegia)
(b) GMFCS levels II (walks with limitations) to IV (limited self-mobility but able to do a standing transfer with the assistance of 1 person);
(c) aged 6 to 16 years;
(d) able to grasp light objects and lift most impaired arm ≥15cm above a table surface;
(e) able to understand instructions and complete testing.

Exclusion Criteria

(a) uncontrolled seizures
(b) had orthopaedic and/or neurological surgery in the six months prior to or scheduled during study period (eligible for inclusion if at least 6 months post-surgery, and/or returned to pre-surgical gross motor and upper limb function following Selective Dorsal Rhizotomy and no longer undergoing post-operative rehabilitation)

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

(d) inability to undertake standing transfers and/or walk a few steps (with a walker).

(e) a significant cognitive and or behavioural impairment limiting the ability to follow instructions determined through discussions with the primary caregiver and/or during a screening assessment.

(f) non-English speaking

Randomisation

A biostatistician will create one central randomization schedule using computer-based random numbers (in blocks of various sizes ranging from 10 to 10), to receive HABIT-ILE immediately or to waitlist usual care. Children will be stratified based on site (QLD, NSW, WA) and GMFCS (II vs. III-IV). After consent and baseline measures are completed, children will be randomised with the use of a REDCap randomisation module, set up by non-study personnel.

Blinding

At all time points, the GMFM-66 and BoHA will be rated from videos[21] by a certified rater masked to both group allocation and timing of assessments. Parents and assessing clinicians will be masked to group allocation for baseline assessments. Analyses will be conducted using coded group allocation.

Study Interventions

The HABIT-ILE and control interventions are summarised according to the Template for Intervention Description and Replication (TIDieR) Checklist[22] in Table 1.

1. HABIT-ILE is a motor learning approach simultaneously addressing coordination of the upper and lower limbs.[23] Key elements of HABIT-ILE:

Dose: The total dose is 65 hours of HABIT-ILE. The 65 hours will be achieved through a two week intensive group-delivered day camp for 6.5 hrs/day over 10 days conducted in the school holidays. Results from our previous research in intensive upper limb training in unilateral CP[24-26] and from our systematic review of all upper limb interventions[8] indicate that 60 hours is likely to be a sufficient dose to achieve significant changes in motor performance, and the two week camps are feasible for children and their families. The model of HABIT-ILE to be tested has been adapted to maximise future clinical translation to ensure acceptability and feasibility to children with bilateral CP and their families in Australia.

Mode: Groups of 8-12 children delivered (1:1 or 2:1 therapist / volunteer / student to child ratio according to ability).

Content and tailoring: Intervention will be based on the child's motor abilities (determined at baseline), age, interests and self-identified functional goals. Tasks/activities are made incrementally more challenging. Practice is structured, using part and whole task practice with high repetition and ongoing feedback about performance.[23,27-28] A process of shaping with progressive approximations is undertaken over the 10 days. For example, if a pincer grasp is required for the goal (e.g. do buttons up on school shirt), and the child is not yet performing this grasp effectively, children will practice tasks that progress incrementally towards this grasp. This requires a clinical reasoning process whereby components/impairments leading to the breakdown of goal performance are identified (e.g. strength, active range of motion, coordination, motor planning or strategy etc.) then targeted with deliberately selected, incrementally challenging games and activities.

Upper extremity: Tasks that will be performed include: (i) incremented table top fine motor activities; (ii) activities of daily living when sitting/standing/walking; (iii) gross motor play and physical activities.

Lower extremity and postural control: Based on the child's baseline motor abilities, postural control/sitting balance will be targeted by sitting on a bench (without postural supports), sitting on an inflated fitness ball, standing with/without upper limb support and/or standing on a balance board. Postural control will be incrementally challenged by increase of duration of sitting or standing, by increasing of inflation of the fitness balls, progression from one mode to a more difficult one (e.g. standing on flat hard surface to standing on balance board), and/or introduction of physical and task demands. Children will also engage in gross motor part and whole practice relevant to their functional goal/s. These may include transfers (sit to stand, floor to stand etc.), stair climbing, walking, running and/or other physical activities.

Intervention providers: A minimum of one physiotherapist and one occupational therapist delivering HABIT-ILE at each site will complete standardised training provided by the developer of HABIT-ILE (YB). This will coincide with the first intensive intervention camp conducted in Brisbane, Australia. The trained therapists

will in turn train and supervise therapy students, volunteers and therapists to deliver HABIT-ILE in the subsequent camps at their site.

Location: The intervention groups will be conducted in the clinics in each of the participating sites.

2. Usual Care: Usual care over the six month wait-list period will vary for children with CP across Australia and can range from weekly clinic-based therapy sessions to school-based consultative services provided on a monthly, quarterly or yearly basis. In order to understand the variability in usual care received, all families in both groups will complete a health resource use questionnaire at baseline and six months post intervention. This will capture the duration of physiotherapy, occupational therapy and any other concurrent medical interventions such as intramuscular Botulinum Toxin A injections and/or serial casting. All children in the usual care group will be offered HABIT-ILE commencing at the subsequent school holiday following the 6 months retention time point (T3).

Adverse events and safety

Any minor or major adverse event associated with HABIT-ILE will be screened on a daily basis by the treating therapist by verbal questioning 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 bike or falling heavily in a game)
- Sore muscles, bruises, other minor injuries not requiring medical treatment
- Feeling upset, guilty, or sad

Major adverse events include:

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

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

Fidelity

<u>Therapist Attributes</u>

It is required that HABIT-ILE therapists at each site 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

It is highly desirable that therapists possess the following attributes:

- 3+ years' experience working with children with CP and their families
- Experience working within models or frameworks of motor learning

Therapist Training

Standardized therapist training will be provided to the core group of therapists (a minimum of one physiotherapist and one occupational therapist from each site) employed to deliver the HABIT-ILE intervention across the three sites. The training package will include:

- Intervention manual/resources
- Onsite training during the first HABIT-ILE camp lead by HABIT-ILE developer (YB)

Training sessions will be video recorded and accessible at any time for established or new therapists delivering the intervention. In subsequent camps, the trained therapists at each site will deliver the one day of training to local site staff and 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 day/second day during each HABIT-ILE camp. Video footage will be reviewed by 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. Manual Abilities Classification System (MACS): The MACS will classify the child's ability to hand objects in daily activities on a 5-level ordinal scale.[33] The MACS has established construct validity, excellent inter-rater reliability (ICC=0.97 between therapists). It is expected that children in the study will be functioning at MACS levels I-III.[33]
2. Gross Motor Function Classification System Expanded and Revised (GMFCS): The GMFCS classifies the child's ability to carry out self-generated

movements related to sitting and walking on a 5-level ordinal scale.[34] The GMFCS has established construct validity, and good inter-rater reliability between therapists.[35]

3. Communication Function Classification System (CFCS): The CFCS will be used to classify children's everyday performance of communicating using all methods (e.g. speech, gestures, eye gaze, augmentative and alternative communication) on a five-level ordinal scale.[36] There is evidence of content validity, good test re-test reliability, good interrater reliability (0.66) between professionals.[36-37]

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

Primary outcomes

1. *ABILHAND-Kids* is a Rasch-built parent completed questionnaire measuring manual ability of children with CP.[38] The ABILHAND-KIDS has demonstrated content, construct and evaluative validity, high internal consistency (α=0.94), excellent test retest reliability (r=0.91)[38] and is responsive in detecting change following intensive upper limb motor training interventions (SDD= 0.81-1.03 logits).[39-40] The ABILHANDS has the strongest evidence of validity and reliability to measure hand function in children with bilateral CP[41] and is responsive to change.[42]
2. The *GMFM-66* is a criterion referenced observation measure developed using Rasch modelling to measure gross motor function of children with CP.[43] The GMFM-66 has established construct validity, high test retest reliability (ICC 0.99)[43] and is responsive to change (MCID=1.5).[43-45]

Secondary outcomes

1. *Brain Structural Integrity:* Brain MRI will be conducted using 3T scanners. The child will be familiarised with the MRI procedures before the scan. During the MRI, the child will watch an age-appropriate movie of their choice, except during the acquisition of the functional MRI. Structural brain images will be acquired using high-resolution 3D T1-weighted MPRAGE and high-resolution 3D T2-weighted FLAIR. Diffusion MRI data will be acquired using a multi-shell approach with 20 directions at b=1000s/mm^2, 60 directions at b=3000s/mm^2

and 8 non-diffusion-weighted images (b=0s/mm^2). The acquisition will be split in 4 blocks (of 22 directions) to allow more efficient rescanning of data affected by motion. Half of the blocks are reverse phase encoded to assist in the correction of residual distortions due to susceptibility inhomogeneity's. Functional MRI data will be acquired using a block design, with a simple active hand and passive foot tapping task. Two 2D gradient recalled echo images (TE1/TE2 4.92/7.38ms) were used to acquire a field map for functional data, which assists when correcting for distortion due to susceptibility inhomogeneities. The total scan time will be <1hour. Structural brain images will be used for lesion scoring using the Fiori scale, a semi-quantitative scale for use in brain imaging of CP.[46] Structural brain images will also be used to assess alterations in cortical thickness in response to therapy. Diffusion data will allow both traditional analysis using the diffusion tensor model (fractional anisotropy and mean diffusivity), as well as state-of-the-art tractography and calculation of advanced imaging microstructural biomarkers thought to closely reflect the status of the underlying brain tissue. fMRI guided tractography will be carried out as described previously.[47-48]

2. *Walking Endurance:* The Six Minute Walk Test is a clinical exercise test measuring walking endurance with excellent test retest reliability (ICC 0.98) for children with CP.[15] The test requires participants to walk as far as possible in six minutes using a 10 meter track with cones demarcating the turning points. Participants will be given verbal and visual instructions before testing. Participants will be instructed to walk as far as possible without running in six minutes. Participants will be given verbal encouragement and every 30 seconds will be advised of the distance covered (in laps) and the time remaining. Distance will be measured to the nearest one-meter mark.
3. *Bimanual Hand Performance:* The Both Hands Assessment (BoHA) measures how children who have bilateral CP use their hands together in bimanual activities.[16] The measure was developed through adaptation of the Assisting Hand Assessment. 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.[17] The test uses a selection of toys to elicit bimanual hand behavior and can be

administered in a structured play session or using the board game version depending on the age of the child. The BoHA takes 15 minutes to complete. The assessment is video-taped for later scoring by a rater blinded to group allocation and who has been certified in its use.

4. *Self-Care and Mobility:* Pediatric Evaluation of Disability Inventory Computerised Assessment Test (PEDI-CAT): The PEDI-CAT is a standardised, norm-referenced assessment of independence in self-care. The test is valid, reliable and responsive in this population.[17] The PEDI-CAT is completed by parents using an iPad or computer application. The item bank of the PEDI-CAT was developed using Rasch measurement modelling on large samples of typically developing children and those with disabilities. Two domains, Self-Care and Mobility will be completed by caregivers.
5. *Performance and satisfaction with occupational performance goals:* The Canadian Occupational Performance Measure (COPM)[18] will be used to measure performance of and satisfaction with individually 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] Children eight years and older can self-report, and caregivers can complete the COPM for younger children or those with cognitive difficulties which would preclude then from completing it independently. Children and their caregivers will set up to three 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.
6. *Quality of life:* The CP-QOL Child is a 52-item, condition-specific self-report measure of child quality of life (QOL) that is specifically developed for measuring QOL in children with CP.[20] The majority of items have the stem "How do you feel about…" with a response scale of 9 points from 1=very unhappy to 9=very happy. The domains covered in the child self-report version include physical wellbeing, social wellbeing, emotional wellbeing, school, and acceptance by others. It has good concurrent validity, internal consistency (Cronbach's alpha 0.80-0.90) and test-retest reliability for children 9 years of age and over. Significant discordance exists between child and parent proxy reports in many health-related QOL instruments and both the child and parent proxy perspectives will be sought in the present study. The

CP-QOL will be completed by all children, unless they are under the age of nine years of have an intellectual disability. An adult who is not participating in the study as the primary parent/caregiver will read the questionnaire alongside the child, and clarify the meaning of the questions and response scale if necessary. For teenagers 13 years of age or older the adolescent version will be completed (CP QOL-Teen) by the teen and their caregiver.[19]

7. *The Child Health Utility Index* (CHU9) is a paediatric health related quality of life measure for use in economic evaluation. The measure consists of nine questions. Children can self-report from seven years of age and parents can proxy report for their child. In this study, the CHU9 will be completed by the child's primary caregiver.[31]

Data Management

Progress notes taken by treating therapists will be fully identified for legal reasons but will be stored confidentially in accordance with professional code of conduct and relevant legislation.

All other information will be coded with a participant ID number. Any identification codes will be stored in a different place from the data records to which they are linked. Data stored in electronic form will also be stored on the Queensland Cerebral Palsy and Rehabilitation Research Centre, The University of Queensland secure server with access limited to Chief Investigators and study coordinator at the Queensland Cerebral Palsy and Rehabilitation Research Centre. De-identified MRI data will be stored on a secure local server at the Australian E-Health Research Centre, CSIRO with access limited to Chief Investigators and named investigators on ethics. All consent forms and identifiable information will be stored in a separate, locked filing cabinet to the research data. Data management will comply with relevant privacy protocols, such as the Australian Standard on personal privacy protection.

Management of withdrawals

Participants can withdraw at any time. Participants who choose to withdraw from the study will not be penalised in any way. If they wish to continue with therapy intervention for their child they will be assisted to source another local therapy option that matches their preferences. 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 can enroll and receive HABIT-ILE

irrespective of whether they consent to the neuroimaging and/or economic analysis aspects of the study. Participants that withdraw will not be replaced, as the a priori power calculation will account for a 10% dropout rate and 10% crossover rate.

Sample Size Estimation

A 1.6 logit change on the ABILHAND kids was achieved in a small RCT of HABIT-ILE.[49] A between-group difference of 1.6 logits was found in a previous controlled trial of HABIT-ILE.[12] A sample of 126 (63 in each arm) yields 80% power, with significance at a two-sided alpha-level of 0.05 to show a difference of 1.6 ABILHAND Kids logits, with a standard deviation of change of 3.0 and buffering for 10% attrition. We will have >90% power to detect a difference of 5 points or greater on the GMFM (assuming SD=6) and alpha=0.05, buffering for 10% attrition). Neuroimaging Outcomes: A 1% change in FA using fMRI guided tractography, and a 6% change in cortical thickness are considered realistic estimates for current therapies. Our recent work on power analysis for imaging-measures of neuroplasticity in CP suggests that, assuming an 80% success rate of MRI, 39 subjects are required to detect a 1% change in FA using fMRI guided tractography, the most sensitive available method.[50]

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) and retention at (T3) based on ABILHAND-KIDS and GMFM scores will be between treatment groups using linear regression with treatment group (HABIT-ILE/waitlist control) included as the main effect and baseline ABILHAND-KIDS as the covariable. Effect estimates will be presented as mean difference and 95% confidence intervals. Secondary analyses will use similar methods to compare outcomes between groups immediately post intervention (T2) for brain structural integrity and structural connectivity (dMRI and fMRI guided tractography), and at T2 and 26 weeks (T3) for clinical outcomes: walking distance, bimanual performance, self-care, mobility, performance of and satisfaction with individualised goals and quality of life. In cases where interval data are not able to be transformed appropriately for regression analyses, non-parametric methods (Mann-Whitney U) will be used for between-treatment comparisons. Sensitivity analyses of all outcomes will be conducted using multiple imputation techniques, to investigate the effect of non-ignorable missing data during follow up.

Health Economics

A within trial cost-utility analysis[29] will be conducted to synthesize the costs and benefits of the HABIT-ILE program compared to usual care. Resource use (staff/student time, equipment and facility use, consumables) associated with the program will be collected alongside the RCT. Health care utilization will be collected using a resource use questionnaire previously used in CP child studies.[30] Health utilities will be derived from the CHU-9D,[31] a generic child quality of life measure designed specifically for economic evaluation, which has been validated in an Australian population.[32] Incremental Cost Effectiveness Ratios (ICERs) will be estimated and where appropriate sensitivity analyses undertaken.

Ethics and dissemination

Full ethical approval has been granted by the Children's Health Queensland Hospital and Health Service Human Research Ethics Committee (HREC/17/QRCH/282), the Medical Research Ethics Committee of The University of Queensland (2018000017/HREC/17/QRCH/2820), and Cerebral Palsy Alliance (2018_04_01/HREC/17/QRCH/282). 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 (ACTRN12618000164291). This protocol is reported according to the Standard Protocol Items: Recommendations for Intervention Trials statement (SPIRIT)[51] and Template for Intervention Description and Replication Checklist (TIDieR).[22]

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 ability to make and keep friends.

Public/Patient Involvement Statement

Patients and public were not involved in the design or conduct of this study. Participants and their families will be informed of progress and outcomes of this study via newsletter and conferences open to consumers.

DISCUSSION

Over 60% of children with CP have bilateral motor impairment, impacting independence in activities of daily living, participation and quality of life. To date,

there is limited evidence for effective interventions to improve motor and functional outcomes in children with bilateral CP. Building on a previous small study,[49] the HABIT-ILE Australia project is the first large-scale study to test the efficacy of this intensive motor training intervention on motor and neuroimaging outcomes children with bilateral cerebral palsy. One potential limitation of the study are that therapy students under the supervision of trained therapists will be primarily delivering the HABIT-ILE intervention. This will be accounted for by providing one day of standardized training for all interventionists, daily debriefing meetings at the end of each day, and ongoing daily feedback from supervising therapists. In addition, fidelity checks with HABIT-ILE developer (YB) will occur throughout the conduct of each HABIT-ILE camp. Secondly, the dose being tested (65 hours) was a pragmatic choice based on what is likely to be feasible and acceptable in the Australian context. This dose, however is less than previous studies (90 hours). This study will additionally determine whether HABIT-ILE is translatable and implementable to a broad Australian setting.

The study has a number of strengths. The number of participants to be included has been calculated for both the primary clinical and secondary neuroimaging outcomes. Selected outcome measures have evidence for both validity and reliability in our population of interest. Development of standardized interventionist training and fidelity monitoring in addition to a with-in trial cost-utility analysis will provide vital information to inform the potential translation of this intervention. It is anticipated that results of this large RCT will be disseminated widely through peer reviewed journals and academic conferences.

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

Acknowledgments

We acknowledge Mika Shimada, Study Clinical Research Coordinator; Megan Thorley, Occupational Therapist, Meredith Winter, Physiotherapist and Kate McLeod, Physiotherapist who are the clinical leads at the Brisbane site; Sherilyn Nolan, Physiotherapist who is the site coordinator for Perth; Bree Harmsen, Occupational Therapist and Marissa Smith, Physiotherapist who are the clinical leads in Perth; Ashleigh Hines, Occupational Therapist who is the site coordinator for Sydney; Anna te Velde, Physiotherapist and Emma Stanton, Occupational Therapist are the clinical

leads at the Sydney site; Julie Paradis, Occupational Therapist Belgium for training and mentorship of Australian therapists in HABIT-ILE; Herston Imaging Facility, Brisbane for performing MRIs at the Brisbane site. I-Med New South Wales for performing the MRIs at the Sydney site.

Competing Interests: None declared

Funding

This work is supported by the National Health and Medical Research Council (NHMRC) for a Project Grant (144846); NHMRC Career Development Fellowship (LS, 1160694); NHMRC Research Fellowship (RB, 1105038).

Author Contributions

LS is the chief investigator together with YB, RB, IN, CE, CM, KP, DR, PG, RW designed, established and achieved funding for this study. LS, SR, IN and CM are responsible for ethics applications and reporting. LS, SR, CM, PG, IN, CE are responsible for recruitment and data collection. YB, LS, SR are responsible for implementation of the interventionist training and fidelity monitoring. KP, JF and RB were responsible for the design and implementation of Neuroimaging outcomes. LS, YB, RB, IN, CE, CM, SR will take the lead roles on preparation for publication of the clinical outcomes; KP, JF, LS, YB and RB will take lead roles on preparation on neuroscience publications; DR, LS and RB will take lead roles of preparation of health economic publications. RW and MC will provide biostatistical advice and oversight for all analyses and publications. LS and the CIs drafted the final version of this manuscript. All authors have contributed to the writing and critical review of the manuscript and have approved the final version. All data from this study will be submitted to peer review journals.

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Table 1: TIDieR checklist[22]: Comparison between HABIT-ILE and traditional "usual care" intervention

Item	Experimental HABIT-ILE	Control traditional "usual care"
Name	Hand Arm Bimanual Intensive Training Including Lower Extremity	Traditional eclectic usual care
Why	Rationale: Intense, repetitive, active motor learning induces activity dependent neuroplasticity. Essential elements: a. Goal directed (goals defined by child/caregiver) b. Motor training with concurrent challenge for upper and lower limbs and posture c. Shaping d. Active practice of goals e. High repetition and intensity	Rationale: Usual care is highly variable, based on biomechanical and neurodevelopmental principles. Elements may include: a. Goals defined either by child/caregiver OR therapist b. Stretching, splinting, casting c. Strengthening d. Functional training (eg. multi-modal joint movements) e. Therapist physically facilitates more typical (normal) movement patterns with children who are passive recipients f. May involve active goal practice
Materials	Therapy bench, fit ball, balance board to intensely and repeatedly challenge posture; activities/toys/games for children to actively develop bimanual hand skills with continuous practice of part and whole tasks. 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, 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 to the child.

How	Clinic setting	Clinic, hospital, home or school setting
How Much	6.5 hours/day for 10 weekdays over a 2 week period (total 65 hours)	Weekly, monthly therapist provided ± home program. Highly variable.
Tailoring	Tailored to the child's individually defined functional goals. Daily review of progress with a view to continually and incrementally increase the challenge	May be generic (e.g. strength training, casting, splinting protocols), but highly variable.
How well	Daily video footage of participants at the day camp will be taken and reviewed by the supervising team and HABIT-ILE developer (YB) every second to third day to ensure delivery of intervention as per protocol.	Detailed survey of parents about intervention approaches used. Contamination is not anticipated as intensive therapy interventions are not frequently available for children with CP.