Move it to improve it (Mitii™): A randomised controlled trial of a novel web-based multi-modal training program for children and adolescents with cerebral palsy

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2013-002853
Article Type:	Protocol
Date Submitted by the Author:	07-Mar-2013
Complete List of Authors:	Boyd, Roslyn; The University of Queensland, Queensland Cerebral Palsy and Rehabilitation Research Centre; Children's Health Queensland, Children's Allied Health Research Mitchell, Louise; The University of Queensland, Queensland Cerebral Palsy and Rehabilitation Research Centre Brisbane; Children's Health Queensland, Children's Allied Health Research James, Sarah; The University of Queensland, Queensland Cerebral Palsy and Rehabilitation Research Centre Brisbane; Children's Health Queensland, Children's Allied Health Research Ziviani, Jenny; Children's Health Queensland, Children's Allied Health Research; The University of Queensland, School of Health and Rehabilitation Sciences Sakzewski, Leanne; The University of Queensland, Queensland Cerebral Palsy and Rehabilitation Research Centre Brisbane; Children's Health Queensland, Children's Allied Health Research Smith, Anthony; The University of Queensland, Centre for Online Health Rose, Stephen; CSIRO, eHealth Cunnington, Ross; The University of Queensland, Queensland Brain Institute; The University of Queensland, School of Psychology Whittingham, Koa; The University of Queensland, Queensland Cerebral palsy Research centre; The University of Queensland, School of Psychology Rasmussen, Betina; Helene Elsass Centre, Kliim-Due, Mette; Helene Elsass Centre, Ware, Robert; The University of Queensland, Queensland Children's Medical Research Institute; The University of Queensland, School of Population Health Comans, Tracey; Griffith University, Griffith Health Institute and School of Medicine Scuffham, Paul; Griffith University, Griffith Health Institute and School of Medicine
Primary Subject Heading:	Paediatrics
Secondary Subject Heading:	Neurology, Research methods
Keywords:	Paediatric neurology < NEUROLOGY, REHABILITATION MEDICINE, Telemedicine < BIOTECHNOLOGY & BIOINFORMATICS

Article type: Protocol paper

Title: Move it to improve it (Mitii™): A randomised controlled trial of a novel web-based multi-modal training program for children and adolescents with cerebral palsy

Short title: Mitii™: Randomised controlled trial of a novel web based program for cerebral palsy

Authors:

Roslyn N Boyd [1,2]

Louise E Mitchell [1,2]

Sarah T James [1,2]

Jenny Ziviani [2, 3]

Leanne Sakzewski [1,2]

Anthony Smith[4]

Stephen Rose[5]

Ross Cunnington [6,7]

Koa Whittingham [1,7]

Betina Rasmussen [8]

Mette Kliim-Due [8]

Robert S Ware[9,10]

Tracey A Comans [11]

Paul A Scuffham [11]

[1] Queensland Cerebral Palsy and Rehabilitation Research Centre, School of Medicine, Faculty of Health Sciences, The University of Queensland, Brisbane, Australia
[2] Children's Allied Health Research, Children's Health Queensland, Herston, Brisbane, Australia
[3] School of Health and Rehabilitation Sciences, The University of Queensland, Brisbane, Australia
[4] Centre for Online Health, University of Queensland, Australia
[5] CSIRO, ICT - Australian e-Health Research Centre, Royal Brisbane and Women's Hospital Centre for Clinical Research, The University of Queensland
[6] Queensland Brain Institute, The University of Queensland, Brisbane, Australia
[7]School of Psychology, The University of Queensland
[8] The Helene Elsass Center, Charlottenlund, Denmark
[9]Queensland Children's Medical Research Institute, The University of Queensland;
[10]School of Population Health, The University of Queensland;
[11] Griffith Health Institute and School of Medicine, Griffith University, Brisbane, Queensland

Email addresses:

RB:r.boyd@uq.edu.au
LM: louise.mitchell@uq.edu.au
SJ: s.james2@uq.edu.au
JZ:j.ziviani@uq.edu.au
LS: l.sakzewski1@uq.edu.au
AS: asmith@uq.edu.au
SR: Stephen.Rose@csiro.au
RC: r.cunnington@uq.edu.au;
KW: koawhittingham@uq.edu.au
BR: br@elsasscenter.dk
MKD: mkd@elsasscenter.dk
RSW: r.ware@sph.uq.edu.au
TC: t.comans@griffith.edu.au
PS: p.scuffham@griffith.edu.au

Corresponding Author: Professor Roslyn Boyd

Address*:* Queensland Cerebral Palsy and Rehabilitation Research Centre, Level 7, Block 6, Royal Brisbane and Women's Hospital, Herston QLD 4029, Australia.

Key words: Cerebral Palsy, Congenital Hemiplegia, Telerehabilitation, Virtual Reality, Physical Activity, Executive Function, Randomized Trial, Protocol.

Funding: Project grant: Foundation for Children Grant (RB; JZ), Queensland Government Smart Futures PhD Scholarship (SJ), Smart Futures Co-Investment Program Grant (RB; JZ, AS, SR, TC, PS); NHMRC Career Development Fellowship (RB, 1037220), NHMRC TRIP Fellowship (LS, 1036183), APA Scholarship (LM)

Target Journal: BMJ Open

Article Summary

'Article focus'

- The main aim of this proposed study is to determine if 20 weeks of intensive Mitii™ training can improve upper-limb activity (unimanual and bimanual), occupational performance and cognitive skills in children and adolescents with CP compared to standard care.
- The secondary aim is to further our understanding of the central neurovascular mechanisms underlying changes in UL function, motor planning, and executive function (using functional magnetic resonance imaging (fMRI) and TMS to measure central activation in the parts of the brain controlling movement).
- It is hypothesized that Mitii™ will be more effective than Usual Care (OT/PT) for children with congential hemiplegia (aged 8-18 years) to improve activity (unimanual capacity and bimanual performance) by a mean difference of 5 points on the Assisting Hand Assessment (AHA) and 10% decrease in time on the Jebsen-Taylor Test of Hand Function (JTTHF), and motor and process skills (AMPS) will improve by 0.5 logit scores following MitiiTM intervention.

'Key messages'

- Persons with cerebral palsy require a lifetime of costly and resource intensive interventions which are often limited by equity of access. With increasing burden being placed on health systems, new methods to deliver intensive rehabilitation therapies are needed.
- Mitii™ is an internet based multi-modal training program comprising upper-limb and cognitive training within the context of meaningful physical activity. This is the first time this new technology will be tested to a randomised trial and it is expected this trial.

'Strengths and limitations'

- This study uses a strong design methodology, utilising a matched paired, waitlist controlled, single blinded randomised trial
- This study will use outcomes measures across all domains of the International Classification of Functioning, Disability and Health Framework (ICF) to test the efficacy of Mitii

ABSTRACT:

Introduction: Persons with cerebral palsy require a lifetime of costly and resource intensive interventions which are often limited by equity of access. With increasing burden being placed on health systems, new methods to deliver intensive rehabilitation therapies are needed. Move it to improve it (Mitii™) is an internet based multi-modal program comprising upper-limb and cognitive training within the context of meaningful physical activity. It can be accessed in the client's home at their convenience. The proposed study aims to test the efficacy of Mitii™ in improving upper-limb function, motor planning, executive function, visual perception and physical activity capacity and performance. Additionally, this study hopes to further our understanding of the central neurovascular mechanisms underlying the proposed changes in response to treatment and determine the cost effectiveness of Mitii™.

Methods and analysis: Children with congenital hemiplegia will be recruited to participate in this waitlist control, matched pairs, single blind randomised trial. Children will be matched at baseline and randomly allocated to receive 20 weeks of 30 minutes of daily Mitii™ training immediately, or waitlist for 20 weeks before receiving the same Mitii™ training (potential total dose=70hours). Outcomes will be assessed at 20 weeks after Mitii™ commencement, and retention effects tested at 40 weeks. The primary outcomes will be the Assessment of Motor and Process Skills (AMPS), bimanual coordination using the Assisting Hand Assessment (AHA), and unimanual upper-limb capacity using the Jebsen Taylor Test of Hand Function (JTTHF). Advanced brain imaging will assess use-dependant neuroplasticity. Measures of body structure and functions, activity, participation and quality of life will be used to assess Mitii™ efficacy across all domains of the International Classification of Functioning, Disability and Health framework.

Dissemination: This paper outlines the hypotheses and outcome measures for a waitlist control, matched pairs, single blind randomised trial to test the efficacy of Mitii™.

Trial Registration: ACTRN12611001174976

BACKGROUND:

Cerebral palsy (CP) describes a group of disorders of the development of movement and posture, causing activity limitations, which are attributed to non-progressive disturbances that occurred in the developing foetal or infant brain. The motor disorders of CP are often accompanied by disturbances of sensation, cognition, perception, behaviour, and/or seizure disorders, and by secondary musculoskeletal problems.[1] In Australia, around 600-700 infants are born with CP each year, making it the most common physical disability in childhood.[2] There remains no cure for CP, meaning that an infant born with this condition will require a lifetime of investigations, interventions and equipment. In 2007, CP was estimated to cost $AUD1.47 billion per annum, equating to a per capita financial burden of AUD$43,431 per person with CP per annum.[3] CP is not only a costly but burdensome condition, impacting the individual, his/her family and society more generally. These impacts highlight the need to optimize health, function and fitness of individuals with CP to reduce costs associated with the condition.

Several intensive therapy approaches delivered by a therapist directly with the child with CP are currently offered to improve upper-limb (UL) function. A systematic review and meta-analysis of all non-surgical upper-limb interventions found some evidence to support these intensive training approaches (e.g. modified Constraint Induced Movement Therapy (mCIMT) and bimanual training (BIM)) to improve the amount of use (effect size [ES]=1.54) and efficiency of movement (ES=0.44) of the impaired arm and new repertoires of hand skills (ES=1.22). Our group recently completed a single blind (evaluator masked) randomized trial (INCITE NHMRC:368500) which directly compared two intensive UL training approaches, mCIMT and BIM to improve unimanual capacity, bimanual performance, societal participation and quality of life.[4] Children attended 60 hours of direct training in groups with either context or method of training over 10 days. In a matched pairs design of 32 pairs of children with congenital hemiplegia (64 children in total) there were minimal differences between the two approaches, both improving activity performance equally in the short term (3wks) with mCIMT yielding greater changes in unimanual capacity at six months.[5,6]

In addition to functional changes children receiving mCIMT had greater and earlier use-dependent neuroplasticity, measured with Transcranial Magnetic Stimulation (TMS) immediately post intervention, than those receiving BIM which was sustained at 6 months.[7] These results suggest that a minimum of 60 hours in a block of training is required to drive neuroplasticity, which has implications for the current dose and intensity of standard training regimens for children with unilateral CP. These findings support the need for training to be intensive, repetitious and incrementally challenging in order to drive neuroplasticity.

The challenge is that while both interventions are effective they are costly and require 60 hours of direct rehabilitation provided by specialist trained occupational therapists (OT) and/or physiotherapists (PT). Implementing direct intensive interventions in specialist settings also potentially limits access to children who live in major metropolitan centres. The reality is that current clinical practice affords children with

unilateral CP only consultative or time-limited therapy following pharmacological intervention (1-12 hours/year). Limited available health resources mean the amount of therapy may be insufficient to drive neuroplastic changes necessary for functional improvements to occur. Alternatives for intensive rehabilitation programs are required. Internet delivered programs and 'active' video games are emerging as a popular modality for paediatric interventions. These systems have the potential to deliver novel, engaging and intensive therapies to children in both metropolitan and more isolated areas where services are limited, in a potentially cost effective manner.

'Active' video games not only have the potential to deliver upper-limb interventions, but also to use otherwise sedentary screen time to promote physical activity. Children today, particularly those with motor disabilities which limit participation in sports or exercise, spend increased time in sedentary screen-based leisure activities, such as watching television or playing sedentary video games. This displaces more active behaviours which in part contributes to obesity and other adverse health outcomes.[8] It is known that children and adolescents with CP are less physically active than their typically developing peers[9, 10], or compared to children with other physical disabilities, such as spina bifida or head injuries.[11] This is an important health promotion consideration as patterns of physical activity acquired during childhood years are more likely to be maintained into adult life, providing the foundation for healthy lifestyle choices.[12] Additionally, for school aged children with CP, interventions including intramuscular Botulinum toxin type-A, casting and surgery usually followed by a limited amount of therapy are common at this age. Success of these interventions should be assessed against all dimensions of the International Classification of Functioning, Disability and Health (ICF)[13], including their impact on physical activity capacity and performance, as well as participation.

Activities of daily living (ADL) (i.e. life tasks required for self-care and self-maintenance) are fundamental in supporting participation across school, home and community environments.[14] Children and adolescents with unilateral CP often experience difficulties with ADL due to their motor and associated difficulties.[15] Performance of ADL tasks is a high priority for parents/guardians.[16] Therapy targeting ADL for children with unilateral CP often involves task specific training to stimulate motor learning.[17] Alternatively, therapy may address deficits in motor and cognitive skills that are considered prerequisites for successful ADL performance. Rehabilitation that involves a combination of upper limb, gross motor, cognitive and visual perceptual training is likely to improve ADL performance. Enhanced ADL ability may increase independence for children and adolescents and reduce the burden of care for parents/guardians.

Underpinning participation in many daily tasks are executive functions. This describes an umbrella term for functions such as planning, working memory, inhibition, mental flexibility, as well as the initiation and monitoring of action.[18] Children with mild CP have demonstrated impairments with executive function in multiple domains.[19] Therapies that not only target improvement in physical impairments but also

components of executive function have the potential to improve a child's performance and participation in more complex activities, including academic school performance.

An effective web based multi-modal training that enhances cognitive and motor abilities using multi-disciplinary virtual trainers may be a cost effective means of delivering therapy and facilitate translation of skills into home and community environments. This has significant implications for equity of access for children in diverse geographical locations. Move it to improve it (Mitii™) is an internet based multi-modal training program comprising upper-limb and cognitive training within the context of meaningful physical activity. Mitii™ detects bodily movements generated by a child using a green tracking band worn on the hand, head or knee. These movements are tracked by a web-camera attached to an internet connected computer. Mitii™ requires no specialist or costly equipment and can be delivered in the client's home. Physiotherapists, occupational therapists and psychologists act as virtual trainers remotely accessing the program to set up a series of 'games' via the program's 'cockpit'. These are graded regularly to deliver an incrementally challenging and individualized program.

The feasibility of delivering Mitii™ has been confirmed in a pilot study of 9 children achieving on average 35 minutes of training daily for 20 weeks (total dose 70 hours).[20] Compliance was high, with an average of 85% of children meeting or exceeding this dose. In a pre-post design, children made significant gains in motor and processing skills, functional strength, endurance, and a range of visual perceptual skills.

METHODS

Aims and Hypotheses

The main aim of this proposed study is to determine if 20 weeks of intensive Mitii™ training can improve upper-limb activity (unimanual and bimanual), occupational performance and cognitive skills in children and adolescents with CP compared to standard care. The secondary aim is to further our understanding of the central neurovascular mechanisms underlying changes in UL function, motor planning, and executive function (using functional magnetic resonance imaging (fMRI) and TMS to measure central activation in the parts of the brain controlling movement). This is an essential next step towards providing effective treatment and sustained outcomes. Further aims are to test the efficacy of Mitii™ across all dimensions of the ICF.

The primary hypothesis to be tested is:

1. In a waitlist randomized controlled trial, Mitii™ will be more effective than Usual Care (OT/PT) for children with congential hemiplegia (aged 8-18 years) to improve activity (unimanual capacity and bimanual performance) by a mean difference of 5 points on the Assisting Hand Assessment (AHA) and 10% decrease in time on the Jebsen-Taylor Test of Hand Function (JTTHF), and motor and process skills (AMPS) will improve by 0.5 logit scores following Mitii™ intervention.

Secondary hypotheses:

Mitii™ will be more effective than usual care at improving:

1. Use dependent neuroplasticity (cortical excitability on TMS) and neurovascular changes (fMRI), which will be more extensive and retained for longer;
2. Visual perception (visual discrimination, visual memory and visual sequential memory);
3. Executive functioning (EF; information processing, attentional control, cognitive flexibility, goal setting, working memory and behavioural manifestations of EF in everyday life) ;
4. Psychological functioning (SDQ);
5. Participation (LIFE-H) for categories of personal care, nutrition, education and recreation;
6. Occupational performance (COPM performance and satisfaction);
7. Functioning and participation domains of quality of life (CP-QOL-Child or CP-QOL-Teen);
8. Functional abilities in self-care and daily activities (MobQues28);
9. Physical activity capacity immediately following Mitii™ training (Functional strength: repeated sit to stand, half-kneel to stand and step up tests; and six-minute walk test);
10. Physical activity performance (ActiGraph®) and greater compliance with the national physical activity recommendations[21, 22];
11. Mitii™ will be more cost-effective compared with Usual Care as shown by resource use and effectiveness based on function (AMPS) and quality of life (CP-QOL).

Ethics

Full ethical approval has been obtained by the Medical Ethics Committee of The University of Queensland (2011000608) and the Royal Children's Hospital Brisbane (HREC/11/QRCH/35). Written and informed consent will be obtained from parents or guardian and all participants over 12 years of age before entering the trial. The proposed Mitii™ clinical trial has been registered with the Australian and New Zealand Clinical Trials registration Trial: ACTRN12611001174976.

Study sample and recruitment

Children and youth with spastic type congenital hemiplegia aged 8-18 years will be recruited across Queensland and New South Wales, Australia. Potential study participants will be identified through a population-based research database, which currently comprises over 1600 children with CP at the Queensland Cerebral Palsy and Rehabilitation Research Centre (QCPRRC), the Queensland Cerebral Palsy Register (ACPR), Queensland CP Health Service and advertising to Occupational Therapists, Physiotherapists and Paediatricians at the Royal Children's Hospital, Brisbane and in the community. The recruitment process will target both publicly funded services and private practitioners with the expectation that the sample will be representative of children with congenital hemiplegia.

Inclusion and exclusion criteria

Children with mild to moderate congenital hemiplegia will be recruited, who are: (i) Gross Motor Function Classification (GMFCS) I or II[23]; Manual Abilities Classification scale (MACS) I, II, III[24]; (ii) aged 8-18 years with sufficient co-operation & cognitive understanding to perform the tasks; and (iii) able to access the internet at home (phone line or internet access). Children will be excluded if they have (i) received upper-limb or lower-limb surgery in the previous 6 months; (ii) unstable epilepsy (i.e. frequent seizures not controlled by medication), or (iii) a respiratory, cardiovascular or other medical condition that would prevent them participating safely in the Mitii™ training. Diagnosis of CP will be confirmed by a paediatrician or clinician and in accordance with published recommendations.[25]

Sample size

Sample size calculation is based on the primary hypothesis comparison between the functional effects of Mitii™ compared to standard care at 20 weeks on the AMPS. This study examines a continuous response variable from matched waitlist control and immediate-intervention participants with 1 waitlist control per immediate-intervention participant. In a previous study of Mitii™ the response within each group was normally distributed with standard deviation 0.58 on the AMPS.[20] To detect a clinically significant difference (0.35 units or greater) between groups with 80% power and alpha=0.05, 44 children are required in each group. Allowing for 10% attrition, the sample size will be 98 subjects.

For hypothesis two, based on our previous randomised trial using 3T fMRI we see activation in the representative cortex for motor studies with good signal to noise ratio. Subject numbers will allow for some loss of information due to subject refusal (10%) and scans where motion is a confounder (10%). With 40 subjects in an analysis of baseline to week 20 changes on fMRI, this study will have 80% power to detect a difference between groups of 0.65 SD. If the supplementary motor area (SMA) is considered, given CV for control subjects performing motor tasks (CV of 11% in PM1 and 35% in SMA)[26], and activation signal of 1.5%, we are able to detect differences in % activation levels over time as small as 0.47.

Design

The efficacy of Mitii™ will be tested using a waitlist control assessor masked randomized trial RCT conducted according to CONSORT guidelines (see Figure 1). Participants will be consented to the study and then matched in pairs. All participants of the study will receive Mitii™ training. Within the pair, each participant will be randomized to either:

a) *Immediate intervention group*: Families return home with Mitii™ equipment and begin training immediately;

Or b) *Waitlist delayed intervention (control) group*: Families continue care as usual for 20 weeks and then return to Brisbane for 1-day re-assessment then receive the same intervention as the immediate intervention group.

Children will not be provided with any concomitant treatments, such as arm splinting, casting or upper limb intramuscular Botulinum Toxin Type-A injections during the baseline to 20 week intervention period. Participants who have received intramuscular Botulinum Toxin Type-A in the upper limb the previous 2 months will have assessments and interventions postponed until after their standard follow up has been completed (usually 6-8 weeks post injection). All concurrent therapies provided by local services duration, frequency and content will be recorded by questionnaire at 20 week follow up.

(Insert Figure 1. CONSORT flowchart around here)

Randomisation

Children will be matched in pairs according to age (within 12 month age bands), gender and level of functional ability based on MACS level at screening. A matched pairs design is the design of choice as it minimises the likelihood of group differences at baseline that has often been present in rehabilitation studies.[27 , 28] Once matching has been achieved, children will be randomised within pairs (one member of each pair to be randomly allocated to each group) from concealed envelopes opened by non-study personnel. The randomisation process will involve randomly allocating a number "1" or "2' to each member of the pair. As each pair is entered, they will be allocated the next consecutive envelope, which will be opened by the non-study personnel who will read and record the treatment allocation from the paper inside the envelope. Treatment allocation will be recorded on a piece of folded paper inside each envelope in random order (either 1:Waitlist 2:Immediate; or 1:Immediate 2:Waitlist, with the sequence being computer generated). Study personnel will be informed of group allocation however participants and their parents/guardians will not be informed of their group allocation until after their baseline assessments.

Blinding

Functional MRI and TMS data will be qualitatively analysed by neurologists masked to group allocation. Paediatric neurologists with fMRI training will independently rate scan quality (0-5), region of activation, change over time and patterns of reorganization. Data on the AHA and MUUL will be rated from video recordings analysed by assessors masked to group allocation and assessment time point.

Adverse events

Any minor and major events associated with the training model will be screened at 20 weeks by open-ended questions.

Study Procedure

Children will attend the Queensland Cerebral Palsy and Rehabilitation Research Centre in Brisbane for 1 day for baseline assessments. Participants in the immediate intervention group will spend an additional day for Mitii™ training and then return home with Mitii™ equipment and commence the training immediately. The delayed intervention (waitlist control) group will continue care as usual for 20 weeks and then return to

Brisbane for 1-day re-assessment and then receive the Mitii™ training and equipment. For each participant, data will be collected at Baseline (T1). For the Immediate intervention group, follow up assessments will be conducted post intervention at 20 weeks post randomization (T2), and then retention (40-weeks post randomization, T3). For the Waitlist group, an additional baseline assessment will be conducted at 20 weeks post randomization (T2), and then post intervention at 20 weeks after commencing the Mitii™ training (40 weeks post randomization, T3). Retention of effects will be collected in the Waitlist group by an additional assessment at 60 weeks post randomisation (T4) (see Figure 1).

Mitii™ intervention

Mitii™ is delivered in the participant's home through an internet connected computer with a web-camera using a cloud server-based interactive training-system employing Adobe® Flash® technology. The system has been developed through collaboration between The Helene Elsass Centre, a private software development company (Head-fitted; Århus, Denmark) and the University of Copenhagen. It has now been made commercially available through collaboration between the Helene Elsass Centre and the Ministry of Research under the name Mitii™ (Move it to improve it; Mitii™ developments, Charlottenlund, Denmark).

A child is initially assessed by a multidisciplinary team (physiotherapist, occupational therapist, and psychologist) to ascertain fine and gross motor skills and cognitive abilities. A de-identified alias account is created for the child in Mitii™ and therapists develop an individually tailored group of tasks/games available in the program. The child then logs onto Mitii™ (through internet access) and completes the activities in his/her own home or local environment. Activities include gross motor control (e.g. unilateral and bilateral upper limb movement, sit-to-stand, balance) as well as cognitive tasks (e.g. matching, ordering, moving and tracking objects) (see Table 1). The combination of upper- and lower-limb gross motor, cognitive and visual perceptual training is designed to have a multi-modal effect by training multiple networks which then enhances performance in each area. It consists of a number of training modules or "games" in which the child has to analyse visual information, solve a cognitive problem (i.e. mathematical question or similar) and respond with a motor act (i.e. bend to pick up needle and pop the balloon with the right answer). The participant interacts with the system through movement of a green tracking band worn on the hands or head. The computer program identifies the movements of the child from video images sampled from a simple web-camera attached to the computer.

Mitii™ training

Participant logs into the Mitii™ website and access their individualized training programs at their convenience, enabling training to be completed at any time. The specific content and progression of the program will be decided from a weekly evaluation of participants' performance. The different modules will be combined uniquely according to the specific cognitive and motor abilities of each child. The level of difficulty can be adjusted by increasing the difficulty of the perceptual (e.g. increasingly complex forms

have to be correctly identified), cognitive (e.g. increasingly difficult mathematical questions) or motor challenges (e.g. child has to do more repetitions or work with higher load). This is completed by therapists (physiotherapist, occupational therapist and psychologists) who are in weekly email contact with the participants and their families. This has the effect that the participants and their parents have a private 'virtual' coach who oversees their training.

A series of individual tasks or games will be combined in a sequence to make a daily program of 30 minutes duration. Mitii™ should be completed for at least 30 minutes daily for six days per week for 20 weeks to provide sufficient training intensity (providing a total dose of 60 hours). Tasks can be divided into those training gross-motor or physical activity (eg. repetitive sit-to-stand exercises) or those combining cognitive or visual perception and an upper limb task (eg. moving the upper limb to solve a mathematic equation). To ensure each participant receives a similar training program, all sequences will comprise approximately 60% cognitive-upper limb and 40% gross-motor training tasks individualized to the child's abilities. Step blocks and balance foam can be added as the child progresses to add additional challenge to the tasks.

(Insert Table 1. Mitii Content around here)

Participant and data management

The percentage of eligible participants successfully recruited, and numbers of eligible participants who choose not to participate will be recorded. Participant retention will be recorded throughout the trial period. All data will be analysed by intention to treat, whereby a participant's assessment from the last available time-point is carried forward in the event of study withdrawal or loss to follow-up. Treatment dose is automatically recorded by the Mitii™ program and will be monitored by the therapists. Where participants are not completing the required dose of Mitii™, they will be alerted via email and efforts will be made to increase compliance (using behaviour enhancing strategies or additional feedback).

Classification measures

a) Classification of the brain lesion

Brain lesion will be classified using a qualitative and quantitative structural MRI classification system. The classification system is based on the presumed timing and nature of the insult that resulted in CP including both genetic and non-genetic aetiologies such as cortical malformations & hypoxic ischaemic injury[29] and a quantitative system to grade the location, extent and severity of the brain lesions with an asymmetry index.[30]

b) Gross Motor Function Classification System (GMFCS)

The GMFCS classifies the child's ability to carry out self-initiated movements related to sitting and

walking across 5 levels.[23] The GMFCS has strong construct validity with the Gross Motor Function Measure (r=0.91)[31] and good inter observer reliability between professionals and between professionals and parents.[32] In this sample of children with hemiplegia, all children will be GMFCS level I (walks without limitations) and II (walks with limitations).

c) Manual Abilities Classification System (MACS)

The MACS classifies the child's ability to handle objects in daily activities on one of 5 levels.[24] The MACs has reported construct validity, and excellent inter-rater reliability (Intraclass Correlation Coefficient [ICC]=0.97 between therapists and ICC=0.96 between therapists and parents).[33] All children in the sample will be MACS level I (able to handle objects easily and successfully), level II (able to handle most objects but with somewhat reduced quality and/or speed of achievement so that alternate ways of performance might be used) or level III (handles objects with difficulty; needs help to prepare and/or modify activities).

d) Anthropometric data

Height will be measured to the nearest 0.5 centimetre while the child is standing with his or her back against a wall.

e) Wechsler Intelligence Scale for Children–Fourth Edition Short Form (WISC-IV SF)

The seven subtest, short-form version of the Wechsler Intelligence Scale for Children fourth edition (WISC-IV) will be used to measure intellectual functioning across four indices: verbal comprehension (VCI), perceptual reasoning (PRI), working memory (WMI), and processing speed (PSI). An overall short form, full scale intellectual functioning (FSIQ) score will be calculated from the index scores. The VCI consists of the Vocabulary and Similarities subtests, the PRI is comprised from Block Design and Matrix Reasoning subtests, the WMI is derived from the Digit Span subtest and the PSI from the Coding and Symbol Search subtests. In the Vocabulary subtest, children will name pictures or provide definitions of words (e.g., "what is a hat"). For Similarities, children will describe how two words that are common objects or represent common concepts are similar (e.g. "in what ways are a cat and mouse alike"). In Block Design, children will reproduce a set of red-and-white blocks either modelled or printed two-dimension geometric patterns within a specified time limit. Matrix Reasoning will involve the child being shown an array of pictures with one missing square and they will need to select the picture that fits the array from five options. In Digit Span, children will repeat a string of verbally presented numbers in both a forward and backward direction. Finally, in Symbol Search, children will visually scan a search group of symbols and indicate whether or not a target symbol is in the search group and in Coding, children will transcribe a digit code. Both of the Symbol Search and Coding tasks need to be rapidly completed within two minutes. Index scores will be converted into scaled scores in accordance with normative data based on the child's age and gender (mean=100, standard deviation[SD]=15).[34, 35] All index scores of the WISV-IV SF have shown moderate to high levels of internal consistency (α=0.87–0.96) and are equivalent to those documented for the full WISV-

IV, with the exception of the WMI which is marginally lower than its full length equivalent.

Neurovascular measures

Neurovascular outcomes will be collected at baseline and 20 weeks.

(a) Whole-brain functional MRI studies:

Functional imaging at 3T on a Siemens MAGNETOM Trio MR scanner will be conducted on the research dedicated scanner at the Centre for Advanced Imaging at the University of Queensland. The 3T scanner provides approximately twice the signal to noise ratio compared to conventional 1.5T scanners which will reduce the time in the scanner and improve the resolution of data collected. Published methods[4] will be utilized for conducting serial fMRI studies preparing in a mock MRI scanner and the motor paradigm will consist of a 2-condition block design (wrist extension compared to rest), visually cued via instructions projected on a screen, timed with an auditory cue for the rate of movement at 2Hz. The task and rest periods are 30 seconds with the activation cycle repeated 4 times.

Children with sufficient comprehension will also complete a complex motor task as an additional task in the scanner. This task is a timing versus sequencing task performed in a block design (two runs of six minutes each), where the subject alternates between a block of single index-finger button-pressing and a block of random sequences of 3-finger button-presses. For the sequence task, visual cues of "123, 321, 213" numbers denote a random sequencing of pushing three buttons with their index, third and fourth fingers on buttons with their dominant hand. This complex task is designed to differentiate activation in the primary motor cortex and different aspects of the basal ganglia circuit. The rationale behind the simple and complex movement is based on previous studies that showed these movements are able to induce activation of the motor cortex and basal ganglia circuits.[36] Notably increased complexity of finger movements increases activation of the basal ganglia circuit, and thus provides an ideal model to utilise fMRI to locate function specific regions of the cortex associated with finger movements.

An additional 5 minutes of resting-state fMRI will also be collected for analysis of functional connectivity (FC). Tasks performed prior to resting-state fMRI can influence functional connectivity.[37] The movements performed in the scanner will be rated for speed, range of motion, ability to isolate and the presence of mirror movements in the contralateral hand. Functional MRI will be acquired using a BOLD acquisition sequence (gradient-recalled-echo (GRE) echo-planar imaging (EPI), repetition time (RT)=3.0s, Echo Time (TE)=30ms, Flip angle=850, Slice thickness=3mm, FOV=216mm, 44 slices, 72 x 72 matrix yielding an in-plane resolution of 3.0mm x 3.0mm). A single set of T2-weighted anatomical, FLAIR and 3D T1 volumes will also be collected. Functional MRI image processing, analysis and visualisation will be performed using iBrain™ software[38] and SPM software (Welcome Dept of Imaging Neuroscience, London, UK). Detailed information about pre-processing and post processing of the fMRI has been published.[4] The

same processing and established analysis of data will be utilised for this proposed Mitii™ project. In addition, temporal autocorrelation will be modelled using a white noise and autoregressive AR(1) model within SPM. Motion correction parameters will be included as covariates.[39] Due to heterogeneity in lesion location and size across participants, group analysis of intra-participant change in activation will be using region of interest with iBrain™ software.[38]

b) Diffusion imaging and structural connectivity

Diffusion-weighted images will be acquired using a twice-refocussed single-shot EPI sequence (64 directions, b-value 3000 s/mm2, 60 contiguous slices with 2.5 mm thickness covering the whole brain, in-plane resolution 2.35 x 2.35 mm, acquisition time approximately 10 minutes). White matter tractography will be performed with MRtrix using probabilistic tractography, with fibre orientations obtained using constrained spherical deconvolution, taking into account the presence of crossing fibres.[40,41] An automated technique has been developed to generate whole brain tractograms, from which individual white matter pathways (e.g. motor and sensory) can be extracted for statistical analysis.[42]

To improve our understanding of cortical plasticity post training, cortical reorganisation will be investigated using a combined fMRI-structural connectivity analysis strategy. In this approach, regions of corticomomtor activation derived from the fMRI analysis (generated post therapy) will be used as target masks for extracting white matter motor pathways. This will enable the identification of all corticomotor networks exhibiting plasticity as a result of the motor training paradigms. Plasticity within these neural circuits will be measured by comparing apparent fibre density (AFD)[43], a quantitative measure of the organisation of WM fibres, derived over the entire pathway. This strategy enables both an anatomical view of cortical reorganisation and quantitative measures of altered connectivity induced by therapy. We also propose to measure plasticity based on an analysis of structural connectivity. In this approach, connectivity matrices will be generated based on parcellation of cortical and subcortical using Freesurfer image analysis suite (http://surfer.nmr.mgh.harvard.edu) and the whole brain tractograms, as outlined above. Hit-testing every streamline with every cortical parcellation will generate the connectivity matrices. Diffusivity indices (Fractional Anisotropy [FA] and Mean Diffusivity [MD]), quantitative markers of the integrity of white matter, will be encoded within the connectome to enable assessment of motor task generated reorganisation.[44,45] Network based statistics (NBS)[46] will be performed between the FA and MD connectomes for the control (CP without intervention) and intervention groups to identify statistically significant cortical networks that are associated with neural reorganization.

c) Transmagnetic stimulation (TMS)

TMS (MAGSTIM 200) will be performed on all participants in both groups at baseline then at 20-22 weeks post intervention. The baseline study will be conducted following fMRI to prevent contamination of fMRI findings by TMS. A figure of 8 TMS coil is used to stimulate the brain and surface EMG electrodes are used to record motor evoked potentials (MEPs) from the target muscles, right and left abductor pollicis

brevis (APB). TMS will be performed at the same time of day to reduce variability. MEPs will be recorded on a Synergy EMG machine using band-pass filtering 10Hz–5kHz, sweep speed 100ms and gain 100 V/div. Auditory EMG feedback will be given to ensure voluntary relaxation of the target muscles during stimulation.

The experimental session will record the following parameters:

i) Motor Threshold (MT): Stimulation will commence at 30% of maximum output and increase in 5% increments until the motor evoked potential (MEP) is established. 1% changes in intensity will then be used to calculate the threshold value. Motor threshold is defined as the lowest level of stimulus intensity which produced a MEP in the target muscle of peak-to-peak amplitude > 100 μV on 50% or more of 10 trials.[47]

(ii) MEP Recruitment Curves: The maximum compound muscle action potential (CMAP) amplitude of the resting APB will be determined by supramaximal stimulation of the median nerve at the wrist. For each participant, the average of the CMAP amplitudes obtained after three stimuli will be calculated as was defined as 100%.[48] MEPs obtained by Single pulse TMS using different randomized stimulus intensities of 110, 120, 130, and 140% MT will be expressed as a percentage of the CMAP in order to obtain recruitment curves.[49] An average of 10 peak-to-peak MEPs recorded for each stimulus intensity will be calculated.

For motor thresholds and recruitment curve measurements, the stimulus will be delivered to the contralateral cerebral hemisphere using the appropriate direction of coil current flow (anticlockwise for left cortical stimulation and clockwise for right cortical stimulation). This will be performed using a flat circular 9 cm diameter magnetic coil (14 cm external diameter) connected to a Magstim stimulator (Magstim, Whitland, Dyfed, United Kingdom). The centre of the coil will be positioned over the vertex and held in a plane tangential to it. The coil will be held in place by a support stand, and its position will be checked regularly through each experiment.

(iii) Ipsilateral Motor Pathways: This will be performed using a figure-of-eight–shaped coil (outer diameter of each loop 70 mm) connected to a Magstim stimulator (Magstim, Whitland, Dyfed, United Kingdom). The coil will be placed tangentially over the ipsilateral hand motor cortex with the handle pointing back and laterally 45° away from the midline at the optimal site for the activation of the APB. This is thought to be the best position for activating the pyramidal cells trans-synaptically and preferentially elicits late I-waves.[50] The direction of current induced in the brain will be anterior to posterior.

Primary outcome measures

a) Assessment of Motor and Process Skills (AMPS)

The AMPS is a standardized, criterion-referenced, observational assessment of the motor abilities of people two years of age and older. An OT evaluates the quality of a person's ADL task performance at the

level of activity and participation in a culturally relevant manner.[51] For the assessment, the patient selects a minimum of two daily activities (e.g. dressing, eating, food preparation) from 116 task options, for which the quality of activity is scored on the degree of exertion, efficacy, confidence and independence in 16 ADL motor and 20 ADL processing skills. The child is also given ratings for overall functioning levels. The performance of children in each of the motor and processing skills is scored from 1-4 (1=deficient performance that impeded the action progression and yielded unacceptable outcomes, through to 4=competent performance that supported the action progression and yielded good outcomes). These raw scores are entered into the AMPS computer-scoring software, and converted through many-faceted Rasch (MFR) analyses into linear ADL motor and ADL process ability measures, ranging from 4 to -3 for motor skills and 3 to -4 for processing skills. Test-retest reliability of the AMPS is high for both motor (r=0.9) and process (r=0.87) skill scales in an adult population.[51] This measure is also very sensitive to change, as it evaluates the smallest possible units of ADL task performance and involves 116 task options which vary in challenge.

b) Assisting Hand Assessment (AHA)

Bimanual performance will be assessed using the AHA. This is a Rasch analysed measure of the effectiveness with which a child with a unilateral impairment makes use of his/her impaired hand in bimanual tasks.[52] The test consists of twenty-two items that are videotaped and each scored on a four point rating scale, yielding a range of scores between 22 and 88. Scaled scores are calculated by transforming the total raw score to a percentage and range from 25 to 100. Rasch analysis allows conversion of these ordinal scores into logits (log odds probability units) which are equal interval measures. Inter-rater and intra-rater reliability is high for summed scores (ICC=0.98 and 0.99 respectively). There are three versions of the AHA; small kids (18 months to 5 years), school kids (6 to 12 years) and an adolescent version in development (>13yrs). Test-retest reliability is high for small kids (ICC=0.99) and school kids (ICC=0.98) and reliability between the two forms (small kids versus school kids) is also high (ICC=0.99).[53] The AHA is responsive to change due to an UL intervention.[54] Investigation of reliability yielded a smallest detectible difference of 3.89 raw scores for the small kids and 3.65 raw scores for the school kids version.[53] The AHA requires standardised training and certification of raters.[52] The AHA will be scored by certified raters who will be masked to group allocation and order of assessment.

c) Jebsen Taylor Test of Hand Function (JTTHF)

Activity limitations will be measured for unimanual capacity using the JTTHF.[55] The JTTHF evaluates speed and dexterity in 6 timed tasks with an individual score for each upper limb. The tasks are of varying complexity and use everyday items to assess grasp and release abilities. The original test designed and validated in adults and typically developing children will be modified with omission of the writing activity and by reducing the maximum allowable time of each task to 2 minutes to both reduce frustration and allow comparison with similar studies in children with congenital hemiplegia.[27, 28, 56] The JTTHF has been shown

to be responsive to change due to an intervention; however there are some difficulties with stability of test-retest performance in the unimpaired limb.[27,28,56,57] There is high inter-rater reliability (ICC=0.82-1.0) for each subtest and test-test reliability with 5 patients and 2 raters (r=0.84-0.85) in an aging adult population.[58] The JTHFT has demonstrated good responsiveness to detect change due to interventions that improve upper limb speed and manipulation.[27]

Secondary outcomes will assess Mitii™ against all dimensions of the ICF:

Body Structure and Function domain

a) Executive Functioning

Executive functioning will be assessed across four domains: attentional control, information processing, cognitive flexibility, and attentional control in accordance with Anderson's paediatric model of executive functioning.[59] A neuropsychological test battery will be utilised to assess these domains comprising of subtests from the Delis-Kaplan Executive Function System (D-KEFS)[60] and the Wechsler Intelligence Scale for Children Fourth Edition (WISC-IV).[35] Behavioural manifestations of executive functioning in everyday life will also be assessed using the Behaviour Rating Inventory of Executive Function (BRIEF).[61] All scores will be converted into scaled scores according to normative data based on the child's age and gender.

i) Colour-Word Interference Test (from the D-KEFS)

The Inhibition condition from the Colour-Word Interference Test will be used to measure attentional control. Children will be required to name the ink colour that colour words are printed in across five rows (e.g., say "red" for the word "blue" printed in red ink). The total time (seconds) taken to complete the task will be the primary outcome measure, with longer time indicative of poorer attentional control. Raw scores will be converted into scaled scores (mean=10, SD=3). Excellent test-retest reliability has been shown for the Colour-Word Interference Test (r= 0.90).[62]

ii) Trail Making Test (from the D-KEFS)

The Number Sequencing condition from the Trail Making Test will be used to measure attentional control and the Number-Letter Switching condition will be used to measure cognitive flexibility. In Number Sequencing, children will connect numbers printed on an A3 sheet in numerical order from 1 – 16, while in Number-Letter Switching, children will be required to switch back and forth between connecting numbers in numerical order and letters in alphabetical order, also printed on an A3 sheet, from 1 – 16 and A – P (e.g., "1-a-2-b-3-c"). The total time (seconds) taken to complete each task will be recorded, with a longer time indicating greater difficulty with attention control or cognitive flexibility. Raw scores will be converted into scaled scores (mean=10, SD=3). Adequate test-retest reliability for Number Sequencing (r= 0.77) and Number-Letter Switching (r=0.20-0.55) has been documented.[62]

iii) Tower Test (from the D-KEFS)

The Tower Test will be used to measure goal setting. Children will move five disks across three pegs to build a target tower as illustrated in a picture within a specified time limit. They will be instructed to use the least number of moves possible to complete the tower, that they can only move one disk at a time and that they must never place a larger disk on top of a smaller disk. The total achievement score, which is based on the total number of moves needed to build the tower, and the total number of rule violations will be used to measure goal setting abilities. The lower the achievement score and the higher the rule violations score indicate greater goal setting difficulties. Raw scores will be converted into scaled scores (mean=10, SD= 3). The Tower Test has a moderate to high level of internal consistency (α=0.43-0.84) and adequate test-retest reliability (r= 0.51).[62]

iv) Digit Span (from the WISC-IV)

Digit Span Backwards is a verbal working memory task that requires children to temporarily store and manipulate information and will be used as a measure of cognitive flexibility. A string of numbers will be given verbally to the children increasing from two digits to eight, and they have to repeat the number string in the reverse order (e.g. if "3-7-2" the child should say "2-7-3"). A score of one is given to each string correctly repeated in reverse order with a lower overall score indicating poorer cognitive flexibility. Raw scores will be converted into scaled scores (mean=10, SD=3). Digit Span Backwards has been shown to have a good internal consistency (α=0.80) and adequate test-retest reliability (r=0.74).[63]

v) Coding (from the WISC-IV)

Coding will be used as a measure of information processing. Children will have to copy simple geometric shapes that are paired with numbers within two minutes. The overall number of correctly copied geometric shapes will be calculated, with a lower number indicating poorer information processing. Raw scores will be converted into scaled scores (mean=10, SD=3). Good internal consistency (α=0.82) and test-retest reliability (r=0.81) for Coding has been shown.[63]

vi) Symbol Search (from the WISC-IV)

Information processing will also be assessed using Symbol Search. Children will visually scan for a target symbols in groups of five symbols and indicate whether the target symbol is in the group by placing a line through the word 'yes' or 'no'. Children will be told to work as fast as they can in two minutes. The total number of correctly identified symbols minus the total number of incorrectly identified symbols will be calculated, with lower scores indicating poorer information processing. Raw scores will be converted into scaled scores (mean=10, SD=3). Symbol search has been documented to have an adequate internal consistency (α=0.79) and a high level of test-retest reliability (r=0.80).[63]

vii) Brief Rating Inventory of Executive Function (BRIEF)

In addition to cognitive measures of executive functioning, behavioural manifestations of executive functions in everyday life will be measured using the BRIEF, an 85 item parent-rated questionnaire. Parents rate items (e.g. "does not think before doing") on a three-point scale ranging from 1 (*never*) to 3 (*often*). Two

index scores will be obtained from the BRIEF: (1) the behavioural regulation index (BRI), which is derived from four subscales: initiate, working memory, plan, organisation of materials and monitor, and; (2) the metacognition index (MCI), which is derived from three subscales: inhibit, shift, and emotional control. The BRI and MCI will then be combined to form an overall global executive composite score (GEC). Raw scores will be converted into *T* scores (mean=50, SD=10), with higher *T* scores indicating a greater level of executive dysfunction. A *T* score of 65 and above, which is 1.5 standard deviations above the mean, will be used as the cut-off for abnormal elevations across all scales.[61] The BRIEF has been found to be ecologically valid measure of executive functioning and has been shown to have good internal consistency (α=0.80 – 0.98) and high test-retest reliability on the BRI (r= 0.92), MCI (r=0.88), and the GEC (r=0.86).[61]

b) Test of Visual Perceptual Skills (TVPS)

The TVPS-3 is comprised of seven subscales: visual discrimination, visual memory, visual spatial relationships, form constancy, visual sequential memory, figure-ground, and visual closure.[64] Performance will be determined by the number of correct answers in each test (maximally 16 in each of 7 tests). Performance will be scaled according to normative data and converted into a percentage score for the age group. The TVPS-3 is a reliable and valid measure of visual perception in persons aged 4 to 18 years.[64]

c) The Melbourne Assessment of Unilateral Upper Limb Function (MUUL)

The MUUL measures both upper limb impairment and quality of upper limb function.[65] It is designed for children aged 5 to 15 years with CP and consists of sixteen criterion-referenced items measuring aspects of reach, grasp, release, and manipulation. The maximum possible raw score is 122, with raw scores being computed into percentage scores. Inter-rater and intra-rater reliability for the MUUL is very high for total test scores (ICC=0.95 and 0.97, respectively) and moderate to high for individual items (ICC=0.69 – 0.91).[66] The MUUL also has good internal consistency (α=0.96).[66] Construct and content validity for the MUUL was established during test development.[66]

d) Lower Limb Functional Strength

Mitii™ will focus on training functional strength therefore assessment of Repetition Maximum (RM) during functional exercise will be used to assess strength. Functional strength will be tested according to the protocol outline by Verschuren et al.[67]

i) Lateral step-up

This is the number of step up repetitions onto a bench during 30 seconds. This is tested with the stool height adjusted to the GMFCS level (I,II=15-20 cm stool). The child stands with the leg being tested on the stool and the non-testing leg on the floor, with feet parallel and shoulder width apart. The child then extends the test leg (on the stool) to within 10˚ of full knee extension, so that the non-test leg is off the ground, then lowers the foot back down to the floor until either the toes or heel touches.[68] This is considered one full cycle. The child should maintain dorsiflexion of the non-test foot and a horizontal pelvis throughout by

keeping hands on hips throughout the test. This is repeated and the number completed within 30 seconds is recorded commencing with the right leg for all children. This is then repeated for the left leg.

ii) Sit-to-stand

This tests the number of sit-to-stand repetitions that can be achieved within 30 seconds, with sit-stand-sit considered a full cycle. The seated position is reached when the knees and hips are in 90˚flexion. Full standing is considered within 15˚ full extensions of the hips and legs. The sit-to-stand must be achieved with arms free and without any support from the chair or the child's body.

iii) Half kneel to stand

This is the number of repetitions of half kneel to stand that can be completed in 30 seconds. The child is positioned in half-kneeling on a mat, with the buttocks clear of the lower leg and/or the floor. The child must then assume a standing position without using the arms or any external support, such as the floor or furniture. Repetitions are counted each time the participant achieves a standing position where both legs and hips are within 15˚ of full extension. This is recorded commencing with the right leg in front, and then repeated with the left leg in front.

For all tests, children will be given 2 practice repetitions per extremity prior to formal testing. Between each practice and testing, 30 seconds rest will be provided. Between tests 180 seconds (3 minutes) rest will be provided. The tests will be assessed in the above order: Lateral step test right, lateral step test left, sit to stand, half kneel to stand right, half kneel to stand left. Children will be instructed to perform as many repetitions as possible in 30 seconds and will be verbally encouraged.

Acceptable inter-tester reliability has been demonstrated for functional strength testing in 25 children with CP ((ICC>0.91; Coefficient of variation (CV)=12.1-22.7%) . Reliability for the tests were strong (Lateral step up ICC=0.94; Sit to stand ICC=0.91; Half kneel to stand ICC=0.93 to 0.96). Mean repetitions for the lateral step up were 13.2 (SD=10.5; standard error of measurement (SEM)=2.4 reps; CV=17.8%) for the left side, and 12.6 (SD=10.4; SEM=2.6 reps; CV=22.7%) for the right side. Mean number of repetitions for the sit to stand was 14.4 (SD=5.0; SEM=2.6 reps; CV=22.7%). Half kneel to stand was less, with an average of 7.5 reps (SD=5.5; SEM=1.1 reps; CV=28.6%) for the left side and 6.0 (SD=5.3; SEM=1.4 reps; CV=39.9%) for the right side.[67]

e) Six Minute Walk Test (6MWT)

The 6MWT is a simple, sub-maximal clinical exercise test which measures the distance walked (6MWD) under controlled conditions over six minutes. The 6MWT has been found to be reliable in independently ambulant adolescents with CP.[69] In this population, test-retest reliability was excellent (ICC=0.98). Percentile curves for the 6MWT have been created, though these were from 1,445 typically developing Chinese children aged 7-16 years.[70] No reference curves for children and adolescents with CP exist. While children with CP may exhibit lower 6MWD compared to typically developing children due to

muscle spasticity, aberrant gait patterns and functional restrictions, GMFCS Levels I and II are able to walk with little to no restrictions therefore one could expect similar test results to a typically developing child. The 6MWT will be performed using standardized verbal encouragement asking the children to walk as fast as possible along a flat, straight, 10m corridor with cones marking the turn-around at each end as per Maher et al.[69]

f) Passive Range of Motion

Upper and lower limb passive range of motion for the unimpaired and impaired side will be assessed by occupational and physiotherapists at baseline.

Activity domain

a) Habitual Physical Activity (HPA)

HPA will be measured using ActiGraph® GT3X+ tri-axial accelerometer (Pensacola, FL). This detects accelerations of a magnitude and frequency with raw acceleration data, proportional to the amount of HPA done by an individual. ActiGraph® units will be fitted during assessment and worn during waking hours for 4 days. After 4 days it will be returned by registered post for data extraction and analysis. An activity diary will be coupled with an ActiGraph® to detect and log accelerations of human movement. Data will be considered for analysis where accelerations are recorded for >4 hrs per day. Analysis will convert counts to activity intensity using Evenson cut points[71] to allow comparison to the national physical activity guidelines.[21,22] The ActiGraph® will also be set up to detect step counts.

The ActiGraph® is a valid instrument to detect HPA in children and adolescents with CP. The ActiGraph® accelerometer is strongly correlated to direct observation during structured activity and free play, and more accurate than heart rate.[72] It has also demonstrated excellent classification accuracy, and Evenson cut points were found to be the most accurate for adolescents with CP.[73] In typically developing children, the reliability of accelerometers has been shown to increase with increased recording days (ICC: 0.45 for 1 days to 0.9 for 8 days).[74] Seasonal variation has been demonstrated with less activity being performed in the winter months (ICC=0.54).[74] Age has also been found to influence reliability, with typically developing primary school aged children participating in more moderate to vigorous physical activity on weekends and exhibiting less day-to-day variability in activity, requiring only 4-5 days monitoring, in contrast to adolescents who exercise less on weekends and require 8 or 9 days of monitoring.[75] Acceptable reliability has been found with 4 days of monitoring (r=0.75-0.78).[76] However, there is no evidence that documents the reliability of the ActiGraph® in children with CP. Children in the present study will be fitted with an ActiGraph® accelerometer to collect 4 days of free living activity after the assessments and training days. Additionally, further work on the reliability of the ActiGraph® in children and adolescents with CP will be conducted. Participants will rest for a 5 minute period and then

conduct selected light, moderate and vigorous assessment tasks, interspersed with 5 minute rest periods in a standardized manner whilst wearing an ActiGraph® monitor and concurrently measuring heart rate and classifying the activity using direct observation. All participants will have the option to undergo this assessment during the assessment and Mitii™ training 2 day visit.

b) Mobility Questionnaire (MobQues)

The MobQues measures mobility of children with CP by assessing amount of difficulty the children have in executing mobility activities. It addresses mobility limitations a child experiences in everyday life and covers a range of severity levels. The MobQues focuses on 47 mobility activities, from which the MobQues47 and the MobQues28 scores can be calculated by scoring 47 or 28 mobility activities, respectively. Response options of the MobQues are: Impossible without help (score 0), very difficult (score 1), somewhat difficult (score 2), slightly difficult (score 3), not difficult at all (score 4).Total scores are calculated by adding all item scores (range 0–4) divided by the maximum possible score and multiplied by 100 to obtain scores on a scale of 0 to 100 (with a low score representing severe limitations in mobility):MobQues47=(Σ item / 188)·100; MobQues28=(Σ item / 112)·100. For research purposes, the shorter version (MobQues28) is recommended due to better measurement properties, whereas the MobQues47 can be used for clinical applications. Content validity of the instrument has been demonstrated as 46 of the 47 test questions relate to the 'mobility' according to the definitions of the ICF. Construct validity was demonstrated as MobQues scores decreased with increasing GMFCS level ($p<0.001$). In a subgroup of 162 children, MobQues score was positively correlated to GMFM-66 (MobQues47, $r=0.75$; MobQues28, $r=0.67$, $p<0.001$).[77] It has also been demonstrated to be a reliable instrument.[78] For the strong inter-rater reliability was found for theMobQues47 (ICC=0.92) and MobQues28 (ICC=0.87). The SEM was 7.8 and 8.9 respectively. As expected, the intra-rater reliability was higher for both MobQues versions (ICC=0.96–0.99; SEM=3.5–4.9).[78] The English version has not yet been cross-validated therefore the results demonstrated may differ slightly to that in an English speaking population. Data sharing has been arranged with the MobQues authors to enable cross cultural validation of this tool. To allow this the MobQues47 clinical version will be used at baseline to obtain a full dataset, and then the MobQues28 will be collected at subsequent assessments. The MobQues28 will be extracted from the baseline assessment to allow comparison across time points.

Participation domain

a) Canadian Occupational Performance Measure (COPM)

Individualised goals will be measured using the COPM to evaluate self-perception of occupational performance over time.[79, 80] The COPM will be administered by one OT with the child/adolescent and parent. The COPM is a standardised individualised, client centred measure that evaluates client's self-

perception of occupational performance. Clients identify areas of difficulty in everyday occupational performance and rate their performance and satisfaction for each problem on a scale from 1 to 10. An average score for performance and satisfaction is calculated. [67] The COPM was designed for all ages and disability groups. There is good evidence of construct, content and criterion validity. The retest reliability of the performance and satisfaction scores on the COPM is high (ICC=0.76-0.89).[80-82] The COPM has demonstrated responsiveness to change in paediatric clinical trials,[83, 84] and a 2 point change on COPM performance has been reported as being clinically significant.[79]

b) Assessment of Life Habits (LIFE-H)

The LIFE-H is designed for children aged 5 to 13 years and measures life habits in home, school and neighbourhood environments.[85, 86] It is a questionnaire completed by the parent/caregiver about the child. The child form is based on an adult version. The long form consists of 197 items divided into 12 categories and includes regular activities (e.g. eating meals, communication, and mobility) and social roles. A weighted score ranging from 0 to 10 is generated for each category and overall total.

Evidence of construct validity and criterion validity, with strong correlations between the LIFE-H and PEDI and Functional Independence Measure for Children (WeeFIM), are established.[85, 87] Adequate to excellent internal consistency (α=0.73–0.90 for categories, 0.97 for daily activities and 0.90 for social roles), intra-rater (ICC=0.83–0.95 for daily activities), inter-rater (ICC=0.8–0.91 for daily activities and ICC=0.63–0.9 for social roles) and test-retest reliability (ICC=0.73 for total score) have also been established.[88] Four categories will be evaluated in this study including nutrition (e.g. mealtime activities), personal care (e.g. dressing), education and recreation. These areas were considered to reflect many of the identified difficulties confronted by children with congenital hemiplegia that might be amenable to the intervention program.

c) Participation and Environment Measure for Children and Youth (PEM-CY)

The PEM-CY is a newly developed, parent-report measure for children aged 5 to 17 years that examines participation and environment across three settings: home, school, and community.[89] No interview is required for administration with parents completing the assessment either online or using a paper based form, which supports its use in this large-scale study. The PEM-CY examines the extent to which young people participate in important activity areas within the home, school and community environments, and the extent to which particular features of these environments are perceived to support or challenge the young person's participation. Evidence of the psychometric properties of this new instrument are limited to date, however data from a sample of 576 young people showed internal consistency was moderate to good (□>0.59) across the scales. Test-retest reliability was moderate to good (ICC>0.58) across a 1-4 week period using the online version of the assessment.[90] The PEM-CY will be collected at baseline.

d) Strengths and Difficulties Questionnaire (SDQ)

The SDQ will be used to measure parents' perceptions of prosocial and difficult behaviours in their

child.[91, 92] The SDQ has a total of 33 items. The first 25 items are divided into 5 scales and assess the frequency of emotional symptoms, conduct problems, inattention/hyperactivity, peer problems and prosocial behaviour (e.g. "considerate of other people's feelings"). These items are rated upon reflection of the last six months on a three-point scale, from zero (*not true*) to two (*certainly true*). A total score for each scale (0-10) and an overall total difficulties score (0-40) will be calculated, with higher scores indicating more distress on all scales except prosocial behaviour. A clinical cut-off of ≥17 will be utilised on the total difficulties score. The total score on the 5 scales and the overall total difficulties score will be utilised as measures of the child's psychological functioning. Moderate to high internal consistency (α=0.73-0.82) and test-retest reliability (*r* =0.77–0.85) has been shown on the overall total difficulties score.[93, 94]

Cerebral Palsy Quality of Life (CPQOL)

QOL will be measured using a condition specific measure, either the CPQOL-Child parent report[95], or for children 9 years or age or older, the CPQOL-Teen.[96] Results of factor analysis demonstrated that the CPQOL measures 7 broad domains of quality of life: social wellbeing and acceptance, functioning, participation, physical health, emotional wellbeing, access to services, pain, impact of disability and family health. The psychometric properties of the CPQOL-Child are excellent, with strong internal consistency (□=0.74-0.92 for parent-proxy report; □=0.80-0.90 for child self-report). Test re-test is adequate (ICC=0.76-0.89) and it is moderately correlated with generic QOL and health (r=0.30-0.51).[97, 98] The CPQOL-Teen, for adolescents aged 13-18 years has strong psychometric properties, with strong internal consistency (□=0.81-0.95 for the primary caregiver report; □=0.84-0.96 for the adolescent self-report) and strong test re-test reliability for adolescents (ICC=0.84-0.87) and for primary caregivers (ICC=0.72-0.92). In terms of validity, all domains of the CPQOL-Teen parent report (r=0.40-46) and adolescent report (r=0.58-0.68) were correlated with a generic QOL instrument.[99]

Environmental and Personal Factors

A study questionnaire was developed to capture demographic information that has been shown in the literature to influence a child's participation. These include family ethnicity, household income, parental education and employment, family structure and supports, and family interests. This will be collected at baseline assessments then any changes measured at subsequent assessments. A measure of social advantage/disadvantage will be derived from postcode of residence using the Index of Relative Socio-economic Advantage/Disadvantage from the Australian Bureau of Statistics.[100] Deciles will be reported on a continuum with lower scores reflecting greater socio-economic disadvantage and higher scores reflecting socio-economic advantage.

Economic Analysis

An economic analysis will be conducted to synthesise health outcomes and costs to both families and health systems. Costs will be obtained for healthcare use (measured through self/proxy reports) and measured directly for the intervention (including the number and duration of visits by the intervention team). Standard costs will be assigned to the resource use (e.g. medical care, allied health visits and diagnostic/investigational services will be assigned a cost according to a fee schedule and medications will be costed based on their description, dosage regimens, and whether or not they are listed on the Pharmaceutical Benefits Schedule). Outcomes will be measured as change in Quality of life from baseline to end of intervention based on the CP-QoL. The base case model timeframe will be 20 weeks consistent with the trial follow up and all costs and outcomes will be extrapolated for at least 10 years, with an annual discount rate of 5% applied to both costs and outcomes, to estimate future expected costs and benefits. Sensitivity analyses will be undertaken around key parameters to assess the effect on results from varying these parameters. These can then be compared with other healthcare interventions and value for money judgments made by policy makers. An incremental cost-effectiveness ratio (i.e. $[\text{cost}_{\text{MiiTii}} - \text{cost}_{\text{usual care}}]/[\text{outcome}_{\text{MiiTii}} - \text{outcome}_{\text{usual care}}]$ will be calculated.

Statistical analysis

Analysis will follow standard principles for RCTs, using two-group comparisons on all participants on an intention-to-treat basis. External and internal validity of results will be checked using baseline and general descriptive information available for all eligible families; comparing the characteristics of families who completed the study with those who enrolled in the study but did not complete, and those who did not enrol. Data from each outcome measure will be summarised for each treatment group and descriptive statistics (frequencies, means, medians, 95% CIs) calculated depending on data distribution. The primary comparison immediately post intervention (20 weeks) will be the AMPS and AHA scores. Outcomes between treatment groups will be compared at follow-up using generalised estimating equations (GEEs), with time (0, 20, 40 weeks) and study group (Mitii™, usual care), as well as a time by group interaction as covariables. We will use the Gaussian family, identity link, and an exchangeable correlation structure. Secondary analyses will compare the outcomes between groups for participation (domains of LIFE-H) and QOL (domains of CP-QOL). For dichotomous outcomes we will compare outcomes between-group outcomes using GEEs with the logistic family and logit link. For continuous variables we shall compare using the Gaussian family and identity link (possibly after transformation, depending on the distribution). The magnitude of BOLD changes between groups will be determined using *iBrain*™: ROI will be delineated for each individual primary motor cortex (PM1), SMA, and ipsilateral motor cortex (PM1ipsi) and active voxels in those regions will be counted. These data will be compared for each region over time using GEEs. In subjects where mirror movements did not occur, lateralisation between ipsi- and contralateral

PM1 will be assessed to determine the incidence and magnitude of brain reorganisation. For TMS data changes in mean MT to TMS from ipsi and contralateral hemispheres will be analysed in each group at each F/U. The probability of ipsilateral projections appearing as a result of each treatment paradigm will also be analysed. Statistical significance will be at $p<0.05$ with adjustment for multiple comparisons, and all analyses will be intention to treat. Sensitivity analyses using imputation techniques will investigate whether the effect estimates are biased as a consequence of non-ignorable missing data.

DISCUSSION:

Current models of rehabilitation for children with CP are costly, limited by inequity of access and often not provided at sufficient intensity to drive neuroplasticity to improve outcomes. An effective web based multi-modal training that enhances motor and cognitive abilities using virtual trainers is likely to be a cost effective means of delivering therapy. It is also likely to lead to better translation of skills into the community as participants are responsible for their own training in the home environment. This study has the potential to establish a new cost-effective evidence-based therapy accessible equally by urban, rural and remote children and their families. Should our hypotheses be correct, Mitii™ has the potential to revolutionize delivery of intensive rehabilitation to children and adolescents with CP.

Competing Interests: The authors declare they have no competing interests.

Authors Contributions: RB, JZ, LS, AS and SR are the chief investigators who designed and established this research study. The content of the therapy program Mitii™ was developed by the Helene Elsass Centre then adapted and modified in English for the Australian study. RB, JZ, LM and ML were responsible for ethics applications and reporting. LM, ML, SR, SJ and HB were responsible for recruitment, data collection, and implementation of the studies. SR, RC and RB were responsible for the design, implementation, data collection, analysis of the Advanced Brain Imaging studies. RB, JZ, LS, LM, SR, HB, SJ will take lead roles on preparation of publications on the clinical outcomes of the study and RB, SR, RC will take lead roles on the neuroscience publications from the study. TC and PS will lead the economic evaluation and associated publications. KW advised on EF assessments and will advise on their interpretation. All authors have read and approved the final manuscript.

REFERENCES

1. Rosenbaum P, Paneth N, Leviton A, et al. A report: the definition and classification of cerebral palsy April 2006. *Dev Med Child Neurol Suppl* 2007;**109**:8-14.
2. Odding E, Roebroeck ME, Stam HJ. The epidemiology of cerebral palsy: incidence, impairments and risk factors. *Disabil Rehabil* 2006;**28**:183-91.
3. Access Economics. The Econonic Impact of Cerebral Palsy in Australia in 2007. Canberra, ACT: Access Economics, 2008.
4. Boyd R, Sakzewski L, Ziviani J, et al. INCITE: A randomised trial comparing constraint induced movement therapy and bimanual training in children with congenital hemiplegia. *BMC Neurol* 2010;**10**:4.
5. 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.
6. Sakzewski L, Ziviani J, Abbott DF, et al. Participation outcomes in a randomized trial of 2 models of upper-limb rehabilitation for children with congenital hemiplegia. *Arch Phys Med Rehabil* 2011;**92**:531-9.
7. Boyd R, Abbott D, Badawi N, et al. Use-dependant neuroplasticity in an RCT of constraint induced movement therapy versus bimanual training for children with congenital hemiplegia [abstract]. *Dev Med Child Neurol* 2010;**52**(Suppl 5):11.
8. Foley L, Maddison R. Use of active video games to increase physical activity in children: a (virtual) reality? *Pediatr Exerc Sci* 2010;**22**:7-20.
9. Maher CA, Williams MT, Olds T, et al. Physical and sedentary activity in adolescents with cerebral palsy. *Dev Med Child Neurol* 2007;**49**:450-7.
10. Zwier JN, van Schie PEM, Becher JG, et al. Physical activity in young children with cerebral palsy. *Disabil Rehabil* 2010;**32**:1501-08.
11. Nelson MC, Neumark-Stzainer D, Hannan PJ, et al. Longitudinal and secular trends in physical activity and sedentary behavior during adolescence. *Pediatrics* 2006;**118**:e1627-34.
12. WHO. Health and Development through Physical Activity and Sport. Geneva: WHO, 2003.
13. WHO. International Classification of Functioning, Disability and Health. Geneva, Switzerland: WHO, 2001.
14. Christiansen C, Baum C, Editors. Occupational Therapy – Overcoming Human Performance Deficits. New Jersey: Slack Incorporated, 1991.
15. Van Zelst BR, Miller MD, Russo RN, et al. Activities of daily living in children with hemiplegic cerebral palsy: a cross-sectional evaluation using the Assessment of Motor and Process Skills. *Dev Med Child Neurol* 2006;**48**:723-7.
16. Cusick A, McIntyre S, Novak I, et al. A comparison of goal attainment scaling and the Canadian Occupational Performance Measure for paediatric rehabilitation research. *Pediatr Rehabil* 2006;**9**:149-57.
17. Krebs HI, Fasoli SE, Dipietro L, et al. Motor Learning Characterizes Habilitation of Children With Hemiplegic Cerebral Palsy. *Neurorehabil Neural Repair* 2012
18. Chan RCK, Shum D, Toulopoulou T, et al. Assessment of executive functions: Review of instruments and identification of critical issues. *Arch Clin Neuropsychol* 2008;**23**:201-16.
19. Bodimeade H, Whittingham K, Lloyd O, et al. Executive function in children and adolescents with the congential hemiplegia type of cerebral palsy [Doctor of Psychology]. The University of Queensland, 2011.
20. Bilde PE, Kliim-Due M, Rasmussen B, et al. Individualized, home-based interactive training of cerebral palsy children delivered through the Internet. *BMC Neurol* 2011;**11**:32.
21. Department of Health and Ageing. Australia's Physical Activity Recommendations for 5-12 year olds. Canberra, 2004.
22. Department of Health and Ageing. Australia's Physical Activity Recommendations for 12-18 year olds. Canberra, 2004.
23. Palisano R, Rosenbaum P, Walter S, et al. Development and reliability of a system to classify gross motor function in children with cerebral palsy. *Dev Med Child Neurol* 1997;**39**:214-23.
24. Eliasson AC, Krumlinde-Sundholm L, Rosblad 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.
25. Badawi N, Watson L, Petterson B, et al. What constitutes cerebral palsy? *Dev Med Child Neurol* 1998;**40**:520-7.
26. Loubinoux I, Carel C, Alary F, et al. Within-session and between-session reproducibility of cerebral sensorimotor activation: a test-retest effect evidenced with functional magnetic resonance imaging. *J Cereb Blood Flow Metab* 2001;**21**:592-607.
27. Charles JR, Wolf SL, Schneider JA, et al. Efficacy of a child-friendly form of constraint-induced movement therapy in hemiplegic cerebral palsy: a randomized control trial. *Dev Med Child Neurol* 2006;**48**:635-42.
28. Gordon AM, Schneider JA, Chinnan A, et al. Efficacy of a hand-arm bimanual intensive therapy (HABIT) in children with hemiplegic cerebral palsy: a randomized control trial. *Dev Med Child Neurol* 2007;**49**:830-38.
29. Krageloh-Mann I, Horber V. The role of magnetic resonance imaging in elucidating the pathogenesis of cerebral palsy: a systematic review. *Dev Med Child Neurol* 2007;**49**:144-51.
30. Guzzetta A, Sinclair K, Clarke D, et al. A novel semi-quantitative scale for classification of brain MRI for children with cerebral palsy [abstract]. *Dev Med Child Neurol* 2010;**52**(Suppl 5):74.

31. Palisano RJ, Hanna SE, Rosenbaum PL, et al. Validation of a model of gross motor function for children with cerebral palsy. *Physical Therapy* 2000;**80**:974-85.
32. Morris C, Galuppi BE, Rosenbaum PL. Reliability of family report for the gross motor function classification system. *Dev Med Child Neurol* 2004;**46**:455-60.
33. Morris C, Kurinczuk JJ, Fitzpatrick R, et al. Reliability of the manual ability classification system for children with cerebral palsy. *Dev Med Child Neurol* 2006;**48**:950-53.
34. Crawford JR, Anderson A, Rankin PM, et al. An index-based short-form of the WISC-IV with accompanying analysis of the reliability and abnormality of differences. *Br J Clin Psychol* 2010;**49**:235-58.
35. Wechsler D. Wechsler Intelligence Scale for Children - fourth edition: administration and scoring manual. New York: Psychological Corporation 2004.
36. Lehericy S, Bardinet E, Tremblay L, et al. Motor control in basal ganglia circuits using fMRI and brain atlas approaches. *Cereb cortex* 2006;**16**:149-61.
37. Waites A, Stanislavsky A, Abbott D, et al. The effect of prior cognitive state on resting state networks measured with functional connectivity. *Hum Brain Mapp* 2005;**24**:59-68.
38. Abbott D, Jackson G. iBrain((R)) - Software for analysis and visualisation of functional MR images. *Neuroimage* 2001;**13**:S59-S59.
39. Frackowiak R, Friston K, Frith C, et al. Human Brain Function. 2nd ed. San Diego: Academic Press, 2003.
40. Tournier JD, Calamante F, Connelly A. Robust determination of the fibre orientation distribution in diffusion MRI: Non-negativity constrained super-resolved spherical deconvolution. *Neuroimage* 2007;**35**:1459-72.
41. Tournier JD, Calamante F, Connelly A. MRtrix: Diffusion tractography in crossing fiber regions. *Int J Imaging Syst Technol* 2012;**22**:53-56.
42. Rose S, Guzzetta A, Pannek K, et al. MRI structural connectivity, disruption of primary sensorimotor pathways, and hand function in cerebral palsy. *Brain Connect* 2011;**1**:309-31.
43. Raffelt D, Tournier JD, Rose S, et al. Apparent Fibre Density: a novel measure for the analysis of diffusion-weighted magnetic resonance images. *Neuroimage* 2012;**59**:3976-399.
44. Rose S, Pannek K, Bell C, et al. Direct evidence of intra- and interhemispheric corticomotor network degeneration in amyotrophic lateral sclerosis: an automated MRI structural connectivity study. *Neuroimage* 2012;**59**:2661-9.
45. Rose S, Rowland T, Pannek K, et al. Structural hemispheric asymmetries in the human precentral gyrus hand representation. *Neuroscience* 2012;**210**:211-21.
46. Zalesky A, Fornito A, Bullmore ET. Network-based statistic: identifying differences in brain networks. *Neuroimage* 2010;**53**:1197-207.
47. Rossini PM, Barker AT, Berardelli A, et al. Noninvasive electrical and magnetic stimulation of the brain, spinal-cord and roots - basic principles and procedures for routine clinical-application. Report of an IFCN committee. *Electroencephalogr Clin Neurophysiol* 1994;**91**:79-92.
48. Facchini S, Muellbacher W, Battaglia F, et al. Focal enhancement of motor cortex excitability during motor imagery: a transcranial magnetic stimulation study. *Acta Neurol Scand* 2002;**105**:146-51.
49. Sohn YH, Kaelin-Lang A, Jung HY, et al. Effect of levetiracetam on human corticospinal excitability. *Neurology* 2001;**57**:858-63.
50. Brasil-Neto JP, Cohen LG, Panizza M, et al. Optimal focal transcranial magnetic activation of the human motor cortex: effects of coil orientation, shape of the induced current pulse, and stimulus intensity. *J Clin Neurophysiol* 1992;**9**:132-36.
51. Fisher A, Bray Jones K. Assessment of Motor and Process Skills. Vol. 1. Development, Standardization, and Administration Manual. 7th ed. Forts Collins, CO: Three Star Press, 2010.
52. Krumlinde-Sundholm L, Eliasson A. Development of the Assisting Hand Assessment: a Rasch-built measure intended for children with unilateral upper limb impairments. *Scan J Occup Ther* 2003;**10**:16-26.
53. Holmefur M, Krumlinde-Sundholm L, Eliasson A. Interrater and intrarater reliability of the assisting hand assessment. *Am J Occup Ther* 2007;**61**:79-84.
54. Holmefur M, Aarts P, Hoare B, et al. Retest and alternate forms reliability of the Assisting Hand Assessment [PhD Thesis]. Karolinska Institutet, 2009.
55. Taylor N, Sand PL, Jebsen RH. Evaluation of hand function in children. *Arch Phys Med Rehabil* 1973;**54**:129-35.
56. Eliasson A, Shaw K, Ponten E, et al. Feasibility of a day-camp model of modified constraint induced movement therapy with and without Botulinum Toxin A injections for children with hemiplegia. *Phys Occup Ther Pediatr* 2009;**29**:311-33.
57. Eliasson AC, Krumlinde-Sundholm L, Shaw K, et al. Effects of constraint-induced movement therapy in young children with hemiplegic cerebral palsy: an adapted model. *Dev Med Child Neurol* 2005;**47**:266-75.
58. Hackel ME, Wolfe GA, Bang SM, et al. Changes in hand function in the aging adult as determined by the Jebsen Test of Hand Function. *Phys Ther* 1992;**72**:373-7.
59. Anderson P. Assessment and development of executive function (EF) during childhood. *Child Neuropsychol* 2002;**8**:71-82.

60. Delis DC, Kaplan E, Kramer JH. Delis-Kaplan Executive Function System (D-KEFS) examiner's manual. San Antonio, TX: The Psychological Corporation. 2001.
61. Gioia G, Isquith P, Guy S, et al. Behavior Rating Inventory of Executive Function. Odessa, FL: Psychological Assessment Resources, 2000.
62. Delis DC, Kaplan E, Kramer JH. Delis-Kaplan Executive Function System (D-KEFS) technical manual. San Antonio, Tx: The Psychological Corporation, 2001.
63. Wechsler D. Wechsler Intelligence Scale for Children - fourth edition: technical and interpretative manual. San Antonio, TX: The Psychological Corporation, 2003.
64. Martin NA. Test of Visual Perceptual Skills. 3rd ed. Novato, CA.: Academic Therapy Publications, 2006.
65. Randall M, Johnson L, Reddihough D. The Melbourne Assessment of Unilateral Upper Limb Function Test: Test administration manual. Melbourne: Royal Children's Hospital, 1999.
66. Randall M, Carlin JB, Chondros P, et al. Reliability of the melbourne assessment of unilateral upper limb function. *Dev Med Child Neurol* 2001;**43**:761-67.
67. Verschuren O, Ketelaar M, Takken T, et al. Reliability of hand-held dynamometry and functional strength tests for the lower extremity in children with Cerebral Palsy. *Disabil Rehabil* 2008;**30**:1358-66.
68. Worrell TW, Borchert B, Erner K, et al. Effect of a lateral step-up exercise protocol on quadriceps and lower extremity performance. *J Orthop Sports Phys Ther* 1993;**18**:646-53.
69. Maher CA, Williams MT, Olds TS. The six-minute walk test for children with cerebral palsy. *Int J Rehabil Res* 2008;**31**:185-8.
70. Li AM, Yin J, Au JT, et al. Standard reference for the six-minute-walk test in healthy children aged 7 to 16 years. *Am J Respir Crit Care Med* 2007;**176**:174-80.
71. Evenson KR, Catellier DJ, Gill K, et al. Calibration of two objective measures of physical activity for children. *J Sports Sci* 2008;**26**:1557-65.
72. Capio CM, Sit CH, Abernethy B. Physical activity measurement using MTI (actigraph) among children with cerebral palsy. *Arch Phys Med Rehabil* 2010;**91**:1283-90.
73. Clanchy KM, Tweedy SM, Boyd RN, et al. Validity of accelerometry in ambulatory children and adolescents with cerebral palsy. *Eur J Appl Physiol* 2011;**111**:2951-9.
74. De Vries SI, Van Hirtum HWJEM, Bakker I, et al. Validity and reproducibility of motion sensors in youth: A systematic update. *Med Sci Sports Exerc* 2009;**41**:818-27.
75. Trost SG, Pate RR, Freedson PS, et al. Using objective physical activity measures with youth: How many days of monitoring are needed? *Med Sci Sports Exerc* 2000;**32**:426-31.
76. Janz KF. Validation of the CSA accelerometer for assessing children's physical activity. *Med Sci Sports Exerc* 1994;**26**:369-75.
77. van Ravesteyn NT, Scholtes VA, Becher JG, et al. Measuring mobility limitations in children with cerebral palsy: content and construct validity of a mobility questionnaire (MobQues). *Dev Med Child Neurol* 2010;**52**:e229-35.
78. Van Ravesteyn NT, Dallmeijer AJ, Scholtes VA, et al. Measuring mobility limitations in children with cerebral palsy: interrater and intrarater reliability of a mobility questionnaire (MobQues). *Dev Med Child Neurol* 2010;**52**:194-9.
79. Law M, Baptiste S, Carswell A, et al. The Canadian Occupational Performance Measure. 3rd ed. Ottawa, Ontario: COAT Publications ACE, 1999.
80. Law M, Polatajko H, Pollock N, et al. Pilot testing of the Canadian Occupational Performance Measure: clinical and measurement issues. *Can J Occup Ther* 1994;**61**:191-7.
81. Dedding C, Cardol M, Eyssen I, et al. Validity of the Canadian occupational performance measure: a client-centred outcome measurement. *Clin Rehabil* 2004;**18**:660-67.
82. McColl M, Paterson M, Davies D, et al. Validity and community utility of the Canadian Occupational Performance Measure. *Can J Occup Ther* 2000;**67**:22-30.
83. Lowe K, Novak I, Cusick A. Low-dose/high-concentration localized botulinum toxin A improves upper limb movement and function in children with hemiplegic cerebral palsy. *Dev Med Child Neurol* 2006;**48**:170-75.
84. Wallen M, O'Flaherty SJ, Waugh MCA. Functional outcomes of intramuscular botulinum toxin type A and occupational therapy in the upper limbs of children with cerebral palsy: A randomized controlled trial. *Arch Phys Med Rehabil* 2004;**88**:1-10.
85. Fougeyrollas P, Noreau L, Lepage C. Assessment of Life Habits, Children Long Form. Quebec.: RIPPH/INDCP, 2002.
86. Marincek C, Buhler C, Knops H, et al., eds. The LIFE-H: Assessment of the quality of social participation; 2001 2001; Slovenia.
87. Noreau L, Lepage C, Boissiere L, et al. Social participation in children with cerebral palsy: measurment issues and applications. *Dev Med Child Neurol* 2004;**45**:43-44.
88. Noreau L, Lepage C, Boissiere L, et al. Measuring participation in children with disabilities using the assessment of life habits. *Dev Med Child Neurol* 2007;**49**:666-71.

89. Coster W, Law M, Bedell G, et al. Development of the participation and environment measure for children and youth: conceptual basis. *Disabil Rehabil* 2012;**34**:238-46.

90. Coster W, Bedell G, Law M, et al. Psychometric evaluation of the Participation and Environment Measure for Children and Youth. *Dev Med Child Neurol* 2011;**53**:1030-7.

91. Goodman R. The Strengths and Difficulties Questionnaire: A research note. *J Child Psychol Psychiatry* 1997;**38**:581-86.

92. Goodman R. The extended version of the Strengths and Difficulties Questionnaire as a guide to psychiatric caseness and consequent burden. *J Child Psychol Psychiatry* 1999;**40**:791-99.

93. Goodman R. Psychometric propeties of the Strengths and Difficulties Questionnaire. *J Am Acad Child Adolesc Psychiatry* 2001;**40**:1337-45.

94. Hawes DJ, Dadds MR. Australian data and psychometric propeties of the Strengths and Difficulties Questionnaire. *Aust N Z J Psychiatry* 2004;**38**:644-51.

95. Waters E, Davis E, Boyd R, et al. Cerebral Palsy Quality of Life Questionnaire for Children (CP QOL-Child) Manual. Melbourne: Deakin University, 2006.

96. Davis E, Shelly A, Waters E, et al. Quality of life of adolescents with cerebral palsy: perspectives of adolescents and parents. *Dev Med Child Neurol* 2009;**51**:193-9.

97. Davis E, Waters E, Mackinnon A, et al. Paediatric quality of life instruments: a review of the impact of the conceptual framework on outcomes. *Dev Med Child Neurol* 2006;**48**:311-8.

98. Waters E, Davis E, Mackinnon A, et al. Psychometric properties of the quality of life questionnaire for children with CP. *Dev Med Child Neurol* 2007;**49**:49-55.

99. Davis E, Mackinnon A, Davern M, et al. Description and psychometric properties of the CP QOL-Teen: a quality of life questionnaire for adolescents with cerebral palsy. *Res Dev Disabil* 2013;**34**:344-52.

100. Australian Bureau of Statistics. Census of Population and Housing: Socio-economic Indexes for Areas (SEIFA), 2006. Canberra: ABS, 2008.

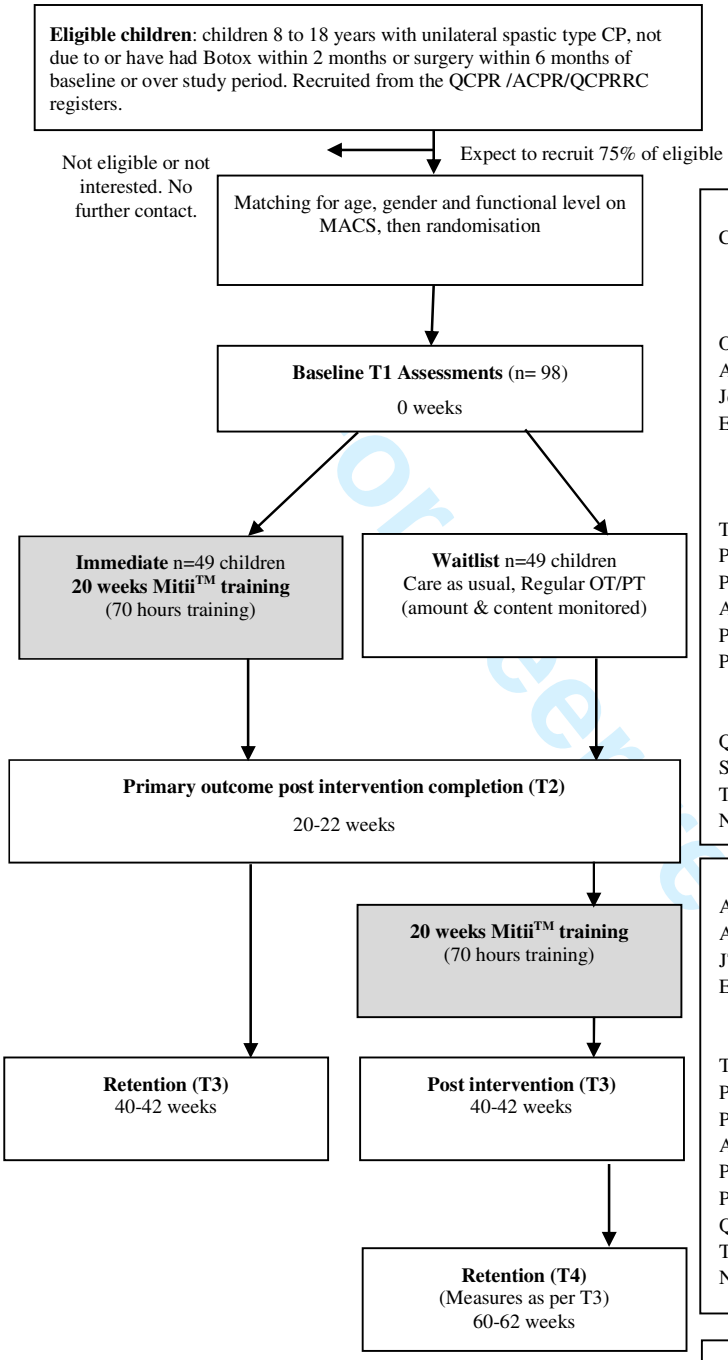
Table 1. Tasks and domains trained within the Mitii™ program and the corresponding actions, parameters that can be manipulated by therapists and results received for each task (Please note: Content of Mitii™ is copyright to Mitii™ Development A/S)

Task	Task description	Action	Parameters adjusted	Domains trained	Results displayed
Memory	Memorise a sequence of images	Look at number of images. Images disappear and client must memories them in order which they were shown. Displays sample of images and uses upper limb movement to re-create sequence	Number of images displayed Number of images in sequence Length of time displayed Complexity of images Position of images Number of Repetitions	Upper limb movement Memory/cognition Visual perception	% Correct Time spent on exercise
Brick	Ability to recognise the outline of a picture	Sequence of images displayed, one of which matches shape. Client uses upper limb to drag corresponding image to shape	Number of images Rotation of figures Position of images Position of shape Number of repetitions Complexity of images	Upper limb movement Memory/cognition Visual perception	% Correct Time spent on exercise
Figure builder	Ability to construct a complete image from smaller pieces	An image is in the middle of screen. Small pieces of this and other images are falling down either side. Use upper limb to reach and drag corresponding piece to recreate image from bottom to top.	Number of images Number of pieces Interval between pieces Speed of falling pieces Number of repetitions Complexity of images	Upper limb movement Memory/cognition Visual perception	Number of pieces missed Time spent on exercise
Figure ground	Ability to pick out a figure from an unorganised background	Large background image presented. Use upper limb to pick up small brick and drag to corresponding place in image.	Time held over correct place Precision of placement Number of repetitions Complexity of background	Upper limb movement Visual perception	Time spent on exercise
Spatial relation	Ability to perceive spatial orientation of a figure	Use upper limb to touch the image in the sequence which differs. (Eg. Pear, Apple, Orange, Car. The car is different.)	Number of images Interval between images Time held over correct image Number of repetitions Complexity of images	Upper limb movement Visual perception	% Correct Time spent on exercise
Visual Closure	Ability to recognise an incomplete figure	Series of incomplete images displayed, and complete single image. Use upper limb to drag incomplete image to complete image. Correct image is one that if complete, would be identical to the presented complete image.	Number of images Position of images Internal between images Time held over correct image Repetitions Complexity of images	Upper limb movement Visual perception	% Correct Time spent on exercise

Balloon mathematics	Ability to complete mathematical calculations	Equation and a number of answer options are presented in balloons. Use upper limb to drag pin and pop balloon with correct answer.	Complexity of equation Number of terms in equation Size of number in equation Time held over correct balloon Time equation displayed Time answer displayed Position of balloons Position of pin Number of repetitions	Upper limb movement Memory/cognition Visual perception	% Correct Time spent on exercise
Combination (2-hand exercise)	Ability to co-ordinated both upper limbs	Series of images presented on both sides. Use both hands to drag two matching items into a circle in the centre of the screen	Number of images presented Number of matching pairs Location of goal circle Size of goal circle Time held on correct image Time held in goal circle Number of repetitions Time bomb Complexity of images	Bimanual upper limb coordination Memory/cognition Visual Perception Time challenge	% Correct Time spent on exercise
Flight simulator	Ability to balance against series of lateral displacements	Use band on head to steer the plane against a series of lateral wind gust disturbances	Airplane speed Wind direction Time of wind gust Strength of wind gust Exercise duration	Balance	Time spent on exercise Balance distribution
Follow	Ability to control gross motor movements and activate larger muscle groups	Use band on head to steer an object around screen	Route of object Speed of object movement Amplitude of object movement Size of object Number of repetitions	Lower limb strength Balance	Time spent on exercise % Correct route
Get up/Get down	Activate larger muscle groups to increase intensity and pulse rate	Use band on head to steer object from top to bottom of screen while doing gross motor movement (eg. Sit to stand, Squat to stand, Lunge to stand, Step on/off block)	Location of object Number of repetitions Time bomb	Lower limb strength Balance Time challenge	Time spent on exercise Time per repetition
Follow the leader	Follow a sequence of movements	Video sequence uploaded and client follows visualising themselves and the video in a split screen view	Video created by therapist therefore can modify	Lower limb strength Balance	
UFO	Ability to control gross motor movements and activate larger muscle groups	Use band on head to steer UFO through a series of tunnels. Requires client to squat/extend knees to control	Route of object Speed of object movement Number of repetitions Time bomb	Lower limb strength Balance Time challenge	Time spent on exercise Accuracy of object path

Move	Activate larger muscle groups to increase intensity and pulse rate	Uses large movement of limbs to inflate a balloon until it bursts	Amplitude of movements Movement direction Duration of movement Number of repetitions	Time spent on exercise % increase of balloon
Additional demands				
Balance	Put on wobble board, reduce base of support (e.g. standing on one leg)			
Strength	Step on/off block			

Figure 1: CONSORT Flow chart of the Mitii™ cerebral palsy study



Baseline Measures (T1)

Classification: Gross Motor Functional Classification System (GMFCS), Manual Abilities Classification System (MACS), Height, Range of Motion, Wechsler Intelligence Scale for Children Fourth Edition (WISC-IV) Short Form
Outcomes: Assessment of Motor and Process Skills (AMPS)
Assisting Hand Assessment (AHA)
Jebsen Taylor Test of Hand Function (JTTHF)
Executive Function: Digit Span, Coding and Symbol Search from WISC-IV; Trail Making Test, Colour-Word Interference Test ,and Tower Test from Delis-Kaplan Executive Function System (D-KEFS); Behavior Rating Inventory of Executive Function (BRIEF)
Test of Visual Perception Skills (TVPS)
Physical Activity Capacity: Functional strength, six-minute walk test (6MWT)
Physical Activity Performance: ActiGraph with activity log
Activity limitations: Mobility Questionnaire (MobQues47)
Psychological Function: Strengths and Difficulties Questionnaire (SDQ)
Participation: Participation and Environment Measure for Children and Youth (PEM-CY), Canadian Occupational Performance Measure (COPM), Assessment of Life Habits (LIFE-H)
Quality of life (QOL): CPQOL- child or teen versions
Study entry questionnaire
Total Assessment time = 4 hours
Neurovascular: fMRI and TMS = 2hrs

Post Intervention outcomes (T2)

AMPS
AHA
JTTHF
Executive Function: Digit Span, Coding and Symbol Search from WISC-IV; Trail Making Test, Colour-Word Interference Test and Tower Test from D-KEFS; BRIEF
TVPS
Physical Activity Capacity: Functional strength, 6MWT
Physical Activity Performance: ActiGraph with activity log
Activity limitations: MobQues28
Psychological Function: SDQ
Participation: COPM, LIFE-H
Quality of life: CPQOL- child or teen versions
Total Assessment time = 4 hours
Neurovascular: fMRI and TMS = 2hrs

Retention outcomes (T3+T4)

AMPS
AHA
JTTHF
Executive Function: Digit Span, Coding and Symbol Search from WISC-IV; Trail Making Test, Colour-Word Interference Test and Tower Test from D-KEFS; BRIEF
TVPS
Physical Activity Capacity: Functional strength, 6MWT
Physical Activity Performance: ActiGraph with activity log
Activity limitations: MobQues28
Psychological Function: SDQ
Participation: COPM, LIFE-H
Quality of life: CPQOL- child or teen versions
Total Assessment time = 3 hours

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	4
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	7
	2b	Specific objectives or hypotheses	7-8
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	9-10
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	N/A
Participants	4a	Eligibility criteria for participants	8
	4b	Settings and locations where the data were collected	10
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	11-12
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	12-25
	6b	Any changes to trial outcomes after the trial commenced, with reasons	N/A
Sample size	7a	How sample size was determined	9
	7b	When applicable, explanation of any interim analyses and stopping guidelines	N/A
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	10
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	10
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	10
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	10
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	10

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	N/A
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	26
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	26
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	Figure 1
	13b	For each group, losses and exclusions after randomisation, together with reasons	N/A
Recruitment	14a	Dates defining the periods of recruitment and follow-up	N/A
	14b	Why the trial ended or was stopped	N/A
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	N/A
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	N/A
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	N/A
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	N/A
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	N/A
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	N/A
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	N/A
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	N/A
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	N/A
Other information			
Registration	23	Registration number and name of trial registry	8
Protocol	24	Where the full trial protocol can be accessed, if available	N/A
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	2

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

BMJ open

Move it to improve it (Mitii™): Study protocol of a randomised controlled trial of a novel web-based multi-modal training program for children and adolescents with cerebral palsy

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2013-002853.R1
Article Type:	Protocol
Date Submitted by the Author:	14-Mar-2013
Complete List of Authors:	Boyd, Roslyn; The University of Queensland, Queensland Cerebral Palsy and Rehabilitation Research Centre; Children's Health Queensland, Children's Allied Health Research Mitchell, Louise; The University of Queensland, Queensland Cerebral Palsy and Rehabilitation Research Centre Brisbane; Children's Health Queensland, Children's Allied Health Research James, Sarah; The University of Queensland, Queensland Cerebral Palsy and Rehabilitation Research Centre Brisbane; Children's Health Queensland, Children's Allied Health Research Ziviani, Jenny; Children's Health Queensland, Children's Allied Health Research; The University of Queensland, School of Health and Rehabilitation Sciences Sakzewski, Leanne; The University of Queensland, Queensland Cerebral Palsy and Rehabilitation Research Centre Brisbane; Children's Health Queensland, Children's Allied Health Research Smith, Anthony; The University of Queensland, Centre for Online Health Rose, Stephen; CSIRO, eHealth Cunnington, Ross; The University of Queensland, Queensland Brain Institute; The University of Queensland, School of Psychology Whittingham, Koa; The University of Queensland, Queensland Cerebral palsy Research centre; The University of Queensland, School of Psychology Ware, Robert; The University of Queensland, Queensland Children's Medical Research Institute; The University of Queensland, School of Population Health Comans, Tracey; Griffith University, Griffith Health Institute and School of Medicine Scuffham, Paul; Griffith University, Griffith Health Institute and School of Medicine
Primary Subject Heading:	Paediatrics
Secondary Subject Heading:	Neurology, Research methods
Keywords:	Paediatric neurology < NEUROLOGY, REHABILITATION MEDICINE, Telemedicine < BIOTECHNOLOGY & BIOINFORMATICS

Article type: Protocol paper

Title: Move it to improve it (Mitii™): Study protocol of a randomised controlled trial of a novel web-based multi-modal training program for children and adolescents with cerebral palsy

Short title: Mitii™: Randomised controlled trial of a novel web based program for cerebral palsy

Authors:

Roslyn N Boyd [1,2]

Louise E Mitchell [1,2]

Sarah T James [1,2]

Jenny Ziviani [2, 3]

Leanne Sakzewski [1,2]

Anthony Smith[4]

Stephen Rose[5]

Ross Cunnington [6,7]

Koa Whittingham [1,7]

Robert S Ware[8,9]

Tracey A Comans [10]

Paul A Scuffham [10]

[1] Queensland Cerebral Palsy and Rehabilitation Research Centre, School of Medicine, Faculty of Health Sciences, The University of Queensland, Brisbane, Australia
[2] Children's Allied Health Research, Children's Health Queensland, Herston, Brisbane, Australia
[3] School of Health and Rehabilitation Sciences, The University of Queensland, Brisbane, Australia
[4] Centre for Online Health, University of Queensland, Australia
[5] CSIRO, ICT - Australian e-Health Research Centre, Royal Brisbane and Women's Hospital Centre for Clinical Research, The University of Queensland
[6] Queensland Brain Institute, The University of Queensland, Brisbane, Australia
[7]School of Psychology, The University of Queensland
[8] Queensland Children's Medical Research Institute, The University of Queensland
[9] School of Population Health, The University of Queensland;
[10] Griffith Health Institute and School of Medicine, Griffith University, Brisbane, Queensland

Email addresses:

RB:r.boyd@uq.edu.au
LM: louise.mitchell@uq.edu.au
SJ: s.james2@uq.edu.au
JZ:j.ziviani@uq.edu.au
LS: l.sakzewski1@uq.edu.au
AS: asmith@uq.edu.au
SR: Stephen.Rose@csiro.au
RC: r.cunnington@uq.edu.au;
KW: koawhittingham@uq.edu.au
RSW: r.ware@sph.uq.edu.au
TC: t.comans@griffith.edu.au
PS: p.scuffham@griffith.edu.au

Corresponding Author: Professor Roslyn Boyd

Address*:* Queensland Cerebral Palsy and Rehabilitation Research Centre, Level 7, Block 6, Royal Brisbane and Women's Hospital, Herston QLD 4029, Australia.

Key words: Cerebral Palsy, Congenital Hemiplegia, Telerehabilitation, Virtual Reality, Physical Activity, Executive Function, Randomized Trial, Protocol.

Target Journal: BMJ Open

Article Summary

'Article focus'

- The main aim of this proposed study is to determine if 20 weeks of intensive Mitii™ training can improve upper-limb activity (unimanual and bimanual), occupational performance and cognitive skills in children and adolescents with CP compared to standard care.
- The secondary aim is to further our understanding of the central neurovascular mechanisms underlying changes in UL function, motor planning, and executive function (using functional magnetic resonance imaging (fMRI) and TMS to measure central activation in the parts of the brain controlling movement).
- It is hypothesized that Mitii™ will be more effective than Usual Care (OT/PT) for children with congential hemiplegia (aged 8-18 years) to improve activity (unimanual capacity and bimanual performance) by a mean difference of 5 points on the Assisting Hand Assessment (AHA) and 10% decrease in time on the Jebsen-Taylor Test of Hand Function (JTTHF), and motor and process skills (AMPS) will improve by 0.5 logit scores following Mitii™ intervention.

'Key messages'

- Persons with cerebral palsy require a lifetime of costly and resource intensive interventions which are often limited by equity of access. With increasing burden being placed on health systems, new methods to deliver intensive rehabilitation therapies are needed.
- Mitii™ is an internet based multi-modal training program comprising upper-limb and cognitive training within the context of meaningful physical activity. This is the first time this new technology will be tested to a randomised trial and it is expected this trial.

'Strengths and limitations'

- This study uses a strong design methodology, utilising a matched paired, waitlist controlled, single blinded randomised trial
- This study will use outcomes measures across all domains of the International Classification of Functioning, Disability and Health Framework (ICF) to test the efficacy of Mitii™

ABSTRACT:

Introduction: Persons with cerebral palsy require a lifetime of costly and resource intensive interventions which are often limited by equity of access. With increasing burden being placed on health systems, new methods to deliver intensive rehabilitation therapies are needed. Move it to improve it (Mitii™) is an internet based multi-modal program comprising upper-limb and cognitive training with physical activity. It can be accessed in the client's home at their convenience. The proposed study aims to test the efficacy of Mitii™ in improving upper-limb function and motor planning. Additionally, this study hopes to further our understanding of the central neurovascular mechanisms underlying the proposed changes and determine the cost effectiveness of Mitii™.

Methods and analysis: Children with congenital hemiplegia will be recruited to participate in this waitlist control, matched pairs, single blind randomised trial. Children will be matched at baseline and randomly allocated to receive 20 weeks of 30 minutes of daily Mitii™ training immediately, or waitlist for 20 weeks before receiving the same Mitii™ training (potential total dose=70hours). Outcomes will be assessed at 20 weeks after Mitii™ commencement, and retention effects tested at 40 weeks. The primary outcomes will be the Assessment of Motor and Process Skills (AMPS), the Assisting Hand Assessment (AHA), and unimanual upper-limb capacity using the Jebsen Taylor Test of Hand Function (JTTHF). Advanced brain imaging will assess use-dependant neuroplasticity. Measures of body structure and functions, activity, participation and quality of life will be used to assess Mitii™ efficacy across all domains of the International Classification of Functioning, Disability and Health framework.

Ethics and Dissemination: This project has received Ethics Approval from the Medical Ethics Committee of The University of Queensland (2011000608) and the Royal Children's Hospital Brisbane (HREC/11/QRCH/35). Findings will be disseminated widely through conference presentations, seminars and peer-reviewed scientific journals.

Trial Registration: ACTRN12611001174976

BACKGROUND:

Cerebral palsy (CP) describes a group of disorders of the development of movement and posture, causing activity limitations, which are attributed to non-progressive disturbances that occurred in the developing foetal or infant brain. The motor disorders of CP are often accompanied by disturbances of sensation, cognition, perception, behaviour, and/or seizure disorders, and by secondary musculoskeletal problems.[1] In Australia, around 600-700 infants are born with CP each year, making it the most common physical disability in childhood.[2] There remains no cure for CP, meaning that an infant born with this condition will require a lifetime of investigations, interventions and equipment. In 2007, CP was estimated to cost $AUD1.47 billion per annum, equating to a per capita financial burden of AUD$43,431 per person with CP per annum.[3] CP is not only a costly but burdensome condition, impacting the individual, his/her family and society more generally. These impacts highlight the need to optimize health, function and fitness of individuals with CP to reduce costs associated with the condition.

Several intensive therapy approaches delivered by a therapist directly with the child with CP are currently offered to improve upper-limb (UL) function. A systematic review and meta-analysis of all non-surgical upper-limb interventions found some evidence to support these intensive training approaches (e.g. modified Constraint Induced Movement Therapy (mCIMT) and bimanual training (BIM)) to improve the amount of use (effect size [ES]=1.54) and efficiency of movement (ES=0.44) of the impaired arm and new repertoires of hand skills (ES=1.22). Our group recently completed a single blind (evaluator masked) randomized trial (INCITE NHMRC:368500) which directly compared two intensive UL training approaches, mCIMT and BIM to improve unimanual capacity, bimanual performance, societal participation and quality of life.[4] Children attended 60 hours of direct training in groups with either context or method of training over 10 days. In a matched pairs design of 32 pairs of children with congenital hemiplegia (64 children in total) there were minimal differences between the two approaches, both improving activity performance equally in the short term (3wks) with mCIMT yielding greater changes in unimanual capacity at six months.[5,6]

In addition to functional changes children receiving mCIMT had greater and earlier use-dependent neuroplasticity, measured with Transcranial Magnetic Stimulation (TMS) immediately post intervention, than those receiving BIM which was sustained at 6 months.[7] These results suggest that a minimum of 60 hours in a block of training is required to drive neuroplasticity, which has implications for the current dose and intensity of standard training regimens for children with unilateral CP. These findings support the need for training to be intensive, repetitious and incrementally challenging in order to drive neuroplasticity.

The challenge is that while both interventions are effective they are costly and require 60 hours of direct rehabilitation provided by specialist trained occupational therapists (OT) and/or physiotherapists (PT). Implementing direct intensive interventions in specialist settings also potentially limits access to children who live in major metropolitan centres. The reality is that current clinical practice affords children with

unilateral CP only consultative or time-limited therapy following pharmacological intervention (1-12 hours/year). Limited available health resources mean the amount of therapy may be insufficient to drive neuroplastic changes necessary for functional improvements to occur. Alternatives for intensive rehabilitation programs are required. Internet delivered programs and 'active' video games are emerging as a popular modality for paediatric interventions. These systems have the potential to deliver novel, engaging and intensive therapies to children in both metropolitan and more isolated areas where services are limited, in a potentially cost effective manner.

'Active' video games not only have the potential to deliver upper-limb interventions, but also to use otherwise sedentary screen time to promote physical activity. Children today, particularly those with motor disabilities which limit participation in sports or exercise, spend increased time in sedentary screen-based leisure activities, such as watching television or playing sedentary video games. This displaces more active behaviours which in part contributes to obesity and other adverse health outcomes.[8] It is known that children and adolescents with CP are less physically active than their typically developing peers[9, 10], or compared to children with other physical disabilities, such as spina bifida or head injuries.[11] This is an important health promotion consideration as patterns of physical activity acquired during childhood years are more likely to be maintained into adult life, providing the foundation for healthy lifestyle choices.[12] Additionally, for school aged children with CP, interventions including intramuscular Botulinum toxin type-A, casting and surgery usually followed by a limited amount of therapy are common at this age. Success of these interventions should be assessed against all dimensions of the International Classification of Functioning, Disability and Health (ICF)[13], including their impact on physical activity capacity and performance, as well as participation.

Activities of daily living (ADL) (i.e. life tasks required for self-care and self-maintenance) are fundamental in supporting participation across school, home and community environments.[14] Children and adolescents with unilateral CP often experience difficulties with ADL due to their motor and associated difficulties.[15] Performance of ADL tasks is a high priority for parents/guardians.[16] Therapy targeting ADL for children with unilateral CP often involves task specific training to stimulate motor learning.[17] Alternatively, therapy may address deficits in motor and cognitive skills that are considered prerequisites for successful ADL performance. Rehabilitation that involves a combination of upper limb, gross motor, cognitive and visual perceptual training is likely to improve ADL performance. Enhanced ADL ability may increase independence for children and adolescents and reduce the burden of care for parents/guardians.

Underpinning participation in many daily tasks are executive functions. This describes an umbrella term for functions such as planning, working memory, inhibition, mental flexibility, as well as the initiation and monitoring of action.[18] Children with mild CP have demonstrated impairments with executive function in multiple domains.[19] Therapies that not only target improvement in physical impairments but also

components of executive function have the potential to improve a child's performance and participation in more complex activities, including academic school performance.

An effective web based multi-modal training that enhances cognitive and motor abilities using multi-disciplinary virtual trainers may be a cost effective means of delivering therapy and facilitate translation of skills into home and community environments. This has significant implications for equity of access for children in diverse geographical locations. Move it to improve it (Mitii™) is an internet based multi-modal training program comprising upper-limb and cognitive training within the context of meaningful physical activity. Mitii™ detects bodily movements generated by a child using a green tracking band worn on the hand, head or knee. These movements are tracked by a web-camera attached to an internet connected computer. Mitii™ requires no specialist or costly equipment and can be delivered in the client's home. Physiotherapists, occupational therapists and psychologists act as virtual trainers remotely accessing the program to set up a series of 'games' via the program's 'cockpit'. These are graded regularly to deliver an incrementally challenging and individualized program.

The feasibility of delivering Mitii™ has been confirmed in a pilot study of 9 children achieving on average 35 minutes of training daily for 20 weeks (total dose 70 hours).[20] Compliance was high, with an average of 85% of children meeting or exceeding this dose. In a pre-post design, children made significant gains in motor and processing skills, functional strength, endurance, and a range of visual perceptual skills.

METHODS

Aims and Hypotheses

The main aim of this proposed study is to determine if 20 weeks of intensive Mitii™ training can improve upper-limb activity (unimanual and bimanual), occupational performance and cognitive skills in children and adolescents with CP compared to standard care. The secondary aim is to further our understanding of the central neurovascular mechanisms underlying changes in UL function, motor planning, and executive function (using functional magnetic resonance imaging (fMRI) and TMS to measure central activation in the parts of the brain controlling movement). This is an essential next step towards providing effective treatment and sustained outcomes. Further aims are to test the efficacy of Mitii™ across all dimensions of the ICF.

The primary hypothesis to be tested is:

1. In a waitlist randomized controlled trial, Mitii™ will be more effective than Usual Care (OT/PT) for children with congential hemiplegia (aged 8-18 years) to improve activity (unimanual capacity and bimanual performance) by a mean difference of 5 points on the Assisting Hand Assessment (AHA) and 10% decrease in time on the Jebsen-Taylor Test of Hand Function (JTTHF), and motor and process skills (AMPS) will improve by 0.5 logit scores following Mitii™ intervention.

Secondary hypotheses:

Mitii™ will be more effective than usual care at improving:

1. Use dependent neuroplasticity (cortical excitability on TMS) and neurovascular changes (fMRI), which will be more extensive and retained for longer;
2. Visual perception (visual discrimination, visual memory and visual sequential memory);
3. Executive functioning (EF; information processing, attentional control, cognitive flexibility, goal setting, working memory and behavioural manifestations of EF in everyday life) ;
4. Psychological functioning (SDQ);
5. Participation (LIFE-H) for categories of personal care, nutrition, education and recreation;
6. Occupational performance (COPM performance and satisfaction);
7. Functioning and participation domains of quality of life (CP-QOL-Child or CP-QOL-Teen);
8. Functional abilities in self-care and daily activities (MobQues28);
9. Physical activity capacity immediately following Mitii™ training (Functional strength: repeated sit to stand, half-kneel to stand and step up tests; and six-minute walk test);
10. Physical activity performance (ActiGraph®) and greater compliance with the national physical activity recommendations[21, 22];
11. Mitii™ will be more cost-effective compared with Usual Care as shown by resource use and effectiveness based on function (AMPS) and quality of life (CP-QOL).

Ethics

Full ethical approval has been obtained by the Medical Ethics Committee of The University of Queensland (2011000608) and the Royal Children's Hospital Brisbane (HREC/11/QRCH/35). Written and informed consent will be obtained from parents or guardian and all participants over 12 years of age by study coordinators and personnel upon entering the trial before matching and randomisation. The proposed Mitii™ clinical trial has been registered with the Australian and New Zealand Clinical Trials registration Trial: ACTRN12611001174976.

Study sample and recruitment

Children and youth with spastic type congenital hemiplegia aged 8-18 years will be recruited across Queensland and New South Wales, Australia. Potential study participants will be identified through a population-based research database, which currently comprises over 1600 children with CP at the Queensland Cerebral Palsy and Rehabilitation Research Centre (QCPRRC), the Queensland Cerebral Palsy Register (QCPR), Queensland CP Health Service and advertising to Occupational Therapists, Physiotherapists and Paediatricians at the Royal Children's Hospital, Brisbane and in the community. The recruitment process will target both publicly funded services and private practitioners with the expectation that the sample will be representative of children with congenital hemiplegia.

Inclusion and exclusion criteria

Children with mild to moderate congenital hemiplegia will be recruited, who are: (i) Gross Motor Function Classification (GMFCS) I or II[23]; Manual Abilities Classification scale (MACS) I, II, III[24]; (ii) aged 8-18 years with sufficient co-operation & cognitive understanding to perform the tasks; and (iii) able to access the internet at home (phone line or internet access). Children will be excluded if they have (i) received upper-limb or lower-limb surgery in the previous 6 months; (ii) unstable epilepsy (i.e. frequent seizures not controlled by medication), or (iii) a respiratory, cardiovascular or other medical condition that would prevent them participating safely in the Mitii™ training. Diagnosis of CP will be confirmed by a paediatrician or clinician and in accordance with published recommendations.[25]

Sample size

Sample size calculation is based on the primary hypothesis comparison between the functional effects of Mitii™ compared to standard care at 20 weeks on the AMPS. This study examines a continuous response variable from matched waitlist control and immediate-intervention participants with 1 waitlist control per immediate-intervention participant. In a previous study of Mitii™ the response within each group was normally distributed with standard deviation 0.58 on the AMPS.[20] To detect a clinically significant difference (0.35 units or greater) between groups with 80% power and alpha=0.05, 44 children are required in each group. Allowing for 10% attrition, the sample size will be 98 subjects. To assist in achieving this sample size, participants will be offered reimbursement of travel expenses and flexible appointment times and locations.

For hypothesis two, based on our previous randomised trial using 3T fMRI we see activation in the representative cortex for motor studies with good signal to noise ratio. Subject numbers will allow for some loss of information due to subject refusal (10%) and scans where motion is a confounder (10%). With 40 subjects in an analysis of baseline to week 20 changes on fMRI, this study will have 80% power to detect a difference between groups of 0.65 SD. If the supplementary motor area (SMA) is considered, given CV for control subjects performing motor tasks (CV of 11% in PM1 and 35% in SMA)[26], and activation signal of 1.5%, we are able to detect differences in % activation levels over time as small as 0.47.

Design

The efficacy of Mitii™ will be tested using a waitlist control assessor masked randomized trial RCT conducted according to CONSORT guidelines (see Figure 1). Participants will be consented to the study and then matched in pairs. All participants of the study will receive Mitii™ training. Within the pair, each participant will be randomized to either:

a) *Immediate intervention group*: Families return home with Mitii™ equipment and begin training immediately; Or b) *Waitlist delayed intervention (control) group*: Families continue care as usual for 20

weeks and then return to Brisbane for 1-day re-assessment then receive the same intervention as the immediate intervention group.

Children will not be provided with any concomitant treatments, such as arm splinting, casting or upper limb intramuscular Botulinum Toxin Type-A injections during the baseline to 20 week intervention period. Participants who have received intramuscular Botulinum Toxin Type-A in the upper limb the previous 2 months will have assessments and interventions postponed until after their standard follow up has been completed (usually 6-8 weeks post injection). All concurrent therapies provided by local services duration, frequency and content will be recorded by questionnaire at 20 week follow up.

(Insert Figure 1. CONSORT flowchart around here)

Randomisation

Children will be matched in pairs according to age (within 12 month age bands), gender and level of functional ability based on MACS level at screening. A matched pairs design is the design of choice as it minimises the likelihood of group differences at baseline that has often been present in rehabilitation studies.[27 , 28] Once matching has been achieved, children will be randomised within pairs (one member of each pair to be randomly allocated to each group) from concealed envelopes opened by non-study personnel. The randomisation process will involve randomly allocating a number "1" or "2' to each member of the pair. As each pair is entered, they will be allocated the next consecutive envelope, which will be opened by the non-study personnel who will read and record the treatment allocation from the paper inside the envelope. Treatment allocation will be recorded on a piece of folded paper inside each envelope in random order (either 1:Waitlist 2:Immediate; or 1:Immediate 2:Waitlist, with the sequence being computer generated). Study personnel will be informed of group allocation however participants and their parents/guardians will not be informed of their group allocation until after their baseline assessments.

Blinding

Functional MRI and TMS data will be qualitatively analysed by neurologists masked to group allocation. Paediatric neurologists with fMRI training will independently rate scan quality (0-5), region of activation, change over time and patterns of reorganization. Data on the AHA and MUUL will be rated from video recordings analysed by assessors masked to group allocation and assessment time point.

Adverse events

Any minor and major events associated with the training model will be screened at 20 weeks by open-ended questions.

Study Procedure

Children will attend the Queensland Cerebral Palsy and Rehabilitation Research Centre in Brisbane for 1 day for baseline assessments. Participants in the immediate intervention group will spend an additional day

for Mitii™ training and then return home with Mitii™ equipment and commence the training immediately. The delayed intervention (waitlist control) group will continue care as usual for 20 weeks and then return to Brisbane for 1-day re-assessment and then receive the Mitii™ training and equipment. For each participant, data will be collected at Baseline (T1). For the Immediate intervention group, follow up assessments will be conducted post intervention at 20 weeks post randomization (T2), and then retention (40-weeks post randomization, T3). For the Waitlist group, an additional baseline assessment will be conducted at 20 weeks post randomization (T2), and then post intervention at 20 weeks after commencing the Mitii™ training (40 weeks post randomization, T3). Retention of effects will be collected in the Waitlist group by an additional assessment at 60 weeks post randomisation (T4) (see Figure 1).

Mitii™ intervention

Mitii™ is delivered in the participant's home through an internet connected computer with a web-camera using a cloud server-based interactive training-system employing Adobe® Flash® technology. The system has been developed through collaboration between The Helene Elsass Centre, a private software development company (Head-fitted; Århus, Denmark) and the University of Copenhagen. It has now been made commercially available through collaboration between the Helene Elsass Centre and the Ministry of Research under the name Mitii™ (Move it to improve it; Mitii™ developments, Charlottenlund, Denmark).

A child is initially assessed by a multidisciplinary team (physiotherapist, occupational therapist, and psychologist) to ascertain fine and gross motor skills and cognitive abilities. A de-identified alias account is created for the child in Mitii™ and therapists develop an individually tailored group of tasks/games available in the program. The child then logs onto Mitii™ (through internet access) and completes the activities in his/her own home or local environment. Activities include gross motor control (e.g. unilateral and bilateral upper limb movement, sit-to-stand, balance) as well as cognitive tasks (e.g. matching, ordering, moving and tracking objects) (see Table 1). The combination of upper- and lower-limb gross motor, cognitive and visual perceptual training is designed to have a multi-modal effect by training multiple networks which then enhances performance in each area. It consists of a number of training modules or "games" in which the child has to analyse visual information, solve a cognitive problem (i.e. mathematical question or similar) and respond with a motor act (i.e. bend to pick up needle and pop the balloon with the right answer). The participant interacts with the system through movement of a green tracking band worn on the hands or head. The computer program identifies the movements of the child from video images sampled from a simple web-camera attached to the computer.

Mitii™ training

Participant logs into the Mitii™ website and access their individualized training programs at their convenience, enabling training to be completed at any time. The specific content and progression of the program will be decided from a weekly evaluation of participants' performance. The different modules will

be combined uniquely according to the specific cognitive and motor abilities of each child. The level of difficulty can be adjusted by increasing the difficulty of the perceptual (e.g. increasingly complex forms have to be correctly identified), cognitive (e.g. increasingly difficult mathematical questions) or motor challenges (e.g. child has to do more repetitions or work with higher load). This is completed by therapists (physiotherapist, occupational therapist and psychologists) who are in weekly email contact with the participants and their families. This has the effect that the participants and their parents have a private 'virtual' coach who oversees their training.

A series of individual tasks or games will be combined in a sequence to make a daily program of 30 minutes duration. Mitii™ should be completed for at least 30 minutes daily for six days per week for 20 weeks to provide sufficient training intensity (providing a total dose of 60 hours). Tasks can be divided into those training gross-motor or physical activity (eg. repetitive sit-to-stand exercises) or those combining cognitive or visual perception and an upper limb task (eg. moving the upper limb to solve a mathematic equation). To ensure each participant receives a similar training program, all sequences will comprise approximately 60% cognitive-upper limb and 40% gross-motor training tasks individualized to the child's abilities. Step blocks and balance foam can be added as the child progresses to add additional challenge to the tasks.

(Insert Table 1. Mitii Content around here)

Participant and data management

The percentage of eligible participants successfully recruited, and numbers of eligible participants who choose not to participate will be recorded. Participant retention will be recorded throughout the trial period. All data will be analysed by intention to treat, whereby a participant's assessment from the last available time-point is carried forward in the event of study withdrawal or loss to follow-up. Treatment dose is automatically recorded by the Mitii™ program and will be monitored by the therapists. Strategies to manage engagement in the program will be discussed with the participant and parent/guardian during their initial Mitii™ training. All participants will receive a Mitii™ rewards chart which segments the 20 week program into four 5 week blocks and allows small rewards to be decided in advance for completing each stage. Other strategies such as parent/guardian involvement, feedback, positive reinforcement and incorporating Mitii™ into the family routine will also be discussed. Therapists will contact participants via email, telephone and Skype to troubleshoot any technical programs and to support engagement.

Classification measures

a) Classification of the brain lesion

Brain lesion will be classified using a qualitative and quantitative structural MRI classification system. The classification system is based on the presumed timing and nature of the insult that resulted in CP including both genetic and non-genetic aetiologies such as cortical malformations & hypoxic ischaemic injury[29] and a quantitative system to grade the location, extent and severity of the brain lesions with an asymmetry index.[30]

b) Gross Motor Function Classification System (GMFCS)

The GMFCS classifies the child's ability to carry out self-initiated movements related to sitting and walking across 5 levels.[23] The GMFCS has strong construct validity with the Gross Motor Function Measure (r=0.91)[31] and good inter observer reliability between professionals and between professionals and parents.[32] In this sample of children with hemiplegia, all children will be GMFCS level I (walks without limitations) and II (walks with limitations).

c) Manual Abilities Classification System (MACS)

The MACS classifies the child's ability to handle objects in daily activities on one of 5 levels.[24] The MACs has reported construct validity, and excellent inter-rater reliability (Intraclass Correlation Coefficient [ICC]=0.97 between therapists and ICC=0.96 between therapists and parents).[33] All children in the sample will be MACS level I (able to handle objects easily and successfully), level II (able to handle most objects but with somewhat reduced quality and/or speed of achievement so that alternate ways of performance might be used) or level III (handles objects with difficulty; needs help to prepare and/or modify activities).

d) Anthropometric data

Height will be measured to the nearest 0.5 centimetre while the child is standing with his or her back against a wall.

e) Wechsler Intelligence Scale for Children–Fourth Edition Short Form (WISC-IV SF)

The seven subtest, short-form version of the Wechsler Intelligence Scale for Children fourth edition (WISC-IV) will be used to measure intellectual functioning across four indices: verbal comprehension (VCI), perceptual reasoning (PRI), working memory (WMI), and processing speed (PSI). An overall short form, full scale intellectual functioning (FSIQ) score will be calculated from the index scores. The VCI consists of the Vocabulary and Similarities subtests, the PRI is comprised from Block Design and Matrix Reasoning subtests, the WMI is derived from the Digit Span subtest and the PSI from the Coding and Symbol Search subtests. In the Vocabulary subtest, children will name pictures or provide definitions of words (e.g., "what is a hat"). For Similarities, children will describe how two words that are common objects or represent common concepts are similar (e.g. "in what ways are a cat and mouse alike"). In Block Design,

children will reproduce a set of red-and-white blocks either modelled or printed two-dimension geometric patterns within a specified time limit. Matrix Reasoning will involve the child being shown an array of pictures with one missing square and they will need to select the picture that fits the array from five options. In Digit Span, children will repeat a string of verbally presented numbers in both a forward and backward direction. Finally, in Symbol Search, children will visually scan a search group of symbols and indicate whether or not a target symbol is in the search group and in Coding, children will transcribe a digit code. Both of the Symbol Search and Coding tasks need to be rapidly completed within two minutes. Index scores will be converted into scaled scores in accordance with normative data based on the child's age and gender (mean=100, standard deviation[SD]=15).[34, 35] All index scores of the WISV-IV SF have shown moderate to high levels of internal consistency (α=0.87–0.96) and are equivalent to those documented for the full WISV-IV, with the exception of the WMI which is marginally lower than its full length equivalent.

Neurovascular measures

Neurovascular outcomes will be collected at baseline and 20 weeks.

(a) Whole-brain functional MRI studies:

Functional imaging at 3T on a Siemens MAGNETOM Trio MR scanner will be conducted on the research dedicated scanner at the Centre for Advanced Imaging at the University of Queensland. The 3T scanner provides approximately twice the signal to noise ratio compared to conventional 1.5T scanners which will reduce the time in the scanner and improve the resolution of data collected. Published methods[4] will be utilized for conducting serial fMRI studies preparing in a mock MRI scanner and the motor paradigm will consist of a 2-condition block design (wrist extension compared to rest), visually cued via instructions projected on a screen, timed with an auditory cue for the rate of movement at 2Hz. The task and rest periods are 30 seconds with the activation cycle repeated 4 times.

Children with sufficient comprehension will also complete a complex motor task as an additional task in the scanner. This task is a timing versus sequencing task performed in a block design (two runs of six minutes each), where the subject alternates between a block of single index-finger button-pressing and a block of random sequences of 3-finger button-presses. For the sequence task, visual cues of "123, 321, 213" numbers denote a random sequencing of pushing three buttons with their index, third and fourth fingers on buttons with their dominant hand. This complex task is designed to differentiate activation in the primary motor cortex and different aspects of the basal ganglia circuit. The rationale behind the simple and complex movement is based on previous studies that showed these movements are able to induce activation of the motor cortex and basal ganglia circuits.[36] Notably increased complexity of finger movements increases activation of the basal ganglia circuit, and thus provides an ideal model to utilise fMRI to locate function specific regions of the cortex associated with finger movements.

An additional 5 minutes of resting-state fMRI will also be collected for analysis of functional connectivity (FC). Tasks performed prior to resting-state fMRI can influence functional connectivity.[37] The movements performed in the scanner will be rated for speed, range of motion, ability to isolate and the presence of mirror movements in the contralateral hand. Functional MRI will be acquired using a BOLD acquisition sequence (gradient-recalled-echo (GRE) echo-planar imaging (EPI), repetition time (RT)=3.0s, Echo Time (TE)=30ms, Flip angle=850, Slice thickness=3mm, FOV=216mm, 44 slices, 72 x 72 matrix yielding an in-plane resolution of 3.0mm x 3.0mm). A single set of T2-weighted anatomical, FLAIR and 3D T1 volumes will also be collected. Functional MRI image processing, analysis and visualisation will be performed using iBrain™ software[38] and SPM software (Welcome Dept of Imaging Neuroscience, London, UK). Detailed information about pre-processing and post processing of the fMRI has been published.[4] The same processing and established analysis of data will be utilised for this proposed Mitii™ project. In addition, temporal autocorrelation will be modelled using a white noise and autoregressive AR(1) model within SPM. Motion correction parameters will be included as covariates.[39] Due to heterogeneity in lesion location and size across participants, group analysis of intra-participant change in activation will be using region of interest with iBrain™ software.[38]

b) Diffusion imaging and structural connectivity

Diffusion-weighted images will be acquired using a twice-refocussed single-shot EPI sequence (64 directions, b-value 3000 s/mm2, 60 contiguous slices with 2.5 mm thickness covering the whole brain, in-plane resolution 2.35 x 2.35 mm, acquisition time approximately 10 minutes). White matter tractography will be performed with MRtrix using probabilistic tractography, with fibre orientations obtained using constrained spherical deconvolution, taking into account the presence of crossing fibres.[40,41] An automated technique has been developed to generate whole brain tractograms, from which individual white matter pathways (e.g. motor and sensory) can be extracted for statistical analysis.[42]

To improve our understanding of cortical plasticity post training, cortical reorganisation will be investigated using a combined fMRI-structural connectivity analysis strategy. In this approach, regions of corticomomtor activation derived from the fMRI analysis (generated post therapy) will be used as target masks for extracting white matter motor pathways. This will enable the identification of all corticomotor networks exhibiting plasticity as a result of the motor training paradigms. Plasticity within these neural circuits will be measured by comparing apparent fibre density (AFD)[43], a quantitative measure of the organisation of WM fibres, derived over the entire pathway. This strategy enables both an anatomical view of cortical reorganisation and quantitative measures of altered connectivity induced by therapy. We also propose to measure plasticity based on an analysis of structural connectivity. In this approach, connectivity matrices will be generated based on parcellation of cortical and subcortical using Freesurfer image analysis suite (http://surfer.nmr.mgh.harvard.edu) and the whole brain tractograms, as outlined above. Hit-testing every streamline with every cortical parcellation will generate the connectivity matrices. Diffusivity indices

(Fractional Anisotropy [FA] and Mean Diffusivity [MD]), quantitative markers of the integrity of white matter, will be encoded within the connectome to enable assessment of motor task generated reorganisation.[44, 45] Network based statistics (NBS)[46] will be performed between the FA and MD connectomes for the control (CP without intervention) and intervention groups to identify statistically significant cortical networks that are associated with neural reorganization.

c) Transmagnetic stimulation (TMS)

TMS (MAGSTIM 200) will be performed on all participants in both groups at baseline then at 20-22 weeks post intervention. The baseline study will be conducted following fMRI to prevent contamination of fMRI findings by TMS. A figure of 8 TMS coil is used to stimulate the brain and surface EMG electrodes are used to record motor evoked potentials (MEPs) from the target muscles, right and left abductor pollicis brevis (APB). TMS will be performed at the same time of day to reduce variability. MEPs will be recorded on a Synergy EMG machine using band-pass filtering 10Hz–5kHz, sweep speed 100ms and gain 100 V/div. Auditory EMG feedback will be given to ensure voluntary relaxation of the target muscles during stimulation.

The experimental session will record the following parameters:

i) Motor Threshold (MT): Stimulation will commence at 30% of maximum output and increase in 5% increments until the motor evoked potential (MEP) is established. 1% changes in intensity will then be used to calculate the threshold value. Motor threshold is defined as the lowest level of stimulus intensity which produced a MEP in the target muscle of peak-to-peak amplitude > 100 μV on 50% or more of 10 trials.[47]

(ii) MEP Recruitment Curves: The maximum compound muscle action potential (CMAP) amplitude of the resting APB will be determined by supramaximal stimulation of the median nerve at the wrist. For each participant, the average of the CMAP amplitudes obtained after three stimuli will be calculated as was defined as 100%.[48] MEPs obtained by Single pulse TMS using different randomized stimulus intensities of 110, 120, 130, and 140% MT will be expressed as a percentage of the CMAP in order to obtain recruitment curves.[49] An average of 10 peak-to-peak MEPs recorded for each stimulus intensity will be calculated.

For motor thresholds and recruitment curve measurements, the stimulus will be delivered to the contralateral cerebral hemisphere using the appropriate direction of coil current flow (anticlockwise for left cortical stimulation and clockwise for right cortical stimulation). This will be performed using a flat circular 9 cm diameter magnetic coil (14 cm external diameter) connected to a Magstim stimulator (Magstim, Whitland, Dyfed, United Kingdom). The centre of the coil will be positioned over the vertex and held in a plane tangential to it. The coil will be held in place by a support stand, and its position will be checked regularly through each experiment.

(iii) Ipsilateral Motor Pathways: This will be performed using a figure-of-eight–shaped coil (outer diameter of each loop 70 mm) connected to a Magstim stimulator (Magstim, Whitland, Dyfed, United Kingdom). The

coil will be placed tangentially over the ipsilateral hand motor cortex with the handle pointing back and laterally 45° away from the midline at the optimal site for the activation of the APB. This is thought to be the best position for activating the pyramidal cells trans-synaptically and preferentially elicits late I-waves.[50] The direction of current induced in the brain will be anterior to posterior.

Primary outcome measures

a) Assessment of Motor and Process Skills (AMPS)

The AMPS is a standardized, criterion-referenced, observational assessment of the motor abilities of people two years of age and older. An OT evaluates the quality of a person's ADL task performance at the level of activity and participation in a culturally relevant manner.[51] For the assessment, the patient selects a minimum of two daily activities (e.g. dressing, eating, food preparation) from 116 task options, for which the quality of activity is scored on the degree of exertion, efficacy, confidence and independence in 16 ADL motor and 20 ADL processing skills. The child is also given ratings for overall functioning levels. The performance of children in each of the motor and processing skills is scored from 1-4 (1=deficient performance that impeded the action progression and yielded unacceptable outcomes, through to 4=competent performance that supported the action progression and yielded good outcomes). These raw scores are entered into the AMPS computer-scoring software, and converted through many-faceted Rasch (MFR) analyses into linear ADL motor and ADL process ability measures, ranging from 4 to -3 for motor skills and 3 to -4 for processing skills. Test-retest reliability of the AMPS is high for both motor (r=0.9) and process (r=0.87) skill scales in an adult population.[51] This measure is also very sensitive to change, as it evaluates the smallest possible units of ADL task performance and involves 116 task options which vary in challenge.

b) Assisting Hand Assessment (AHA)

Bimanual performance will be assessed using the AHA. This is a Rasch analysed measure of the effectiveness with which a child with a unilateral impairment makes use of his/her impaired hand in bimanual tasks.[52] The test consists of twenty-two items that are videotaped and each scored on a four point rating scale, yielding a range of scores between 22 and 88. Scaled scores are calculated by transforming the total raw score to a percentage and range from 25 to 100. Rasch analysis allows conversion of these ordinal scores into logits (log odds probability units) which are equal interval measures. Inter-rater and intra-rater reliability is high for summed scores (ICC=0.98 and 0.99 respectively). There are three versions of the AHA; small kids (18 months to 5 years), school kids (6 to 12 years) and an adolescent version in development (>13yrs). Test-retest reliability is high for small kids (ICC=0.99) and school kids (ICC=0.98) and reliability between the two forms (small kids versus school kids) is also high (ICC=0.99).[53] The AHA is responsive to change due to an UL intervention.[54] Investigation of reliability yielded a smallest detectible

difference of 3.89 raw scores for the small kids and 3.65 raw scores for the school kids version.[53] The AHA requires standardised training and certification of raters.[52] The AHA will be scored by certified raters who will be masked to group allocation and order of assessment.

c) Jebsen Taylor Test of Hand Function (JTTHF)

Activity limitations will be measured for unimanual capacity using the JTTHF.[55] The JTTHF evaluates speed and dexterity in 6 timed tasks with an individual score for each upper limb. The tasks are of varying complexity and use everyday items to assess grasp and release abilities. The original test designed and validated in adults and typically developing children will be modified with omission of the writing activity and by reducing the maximum allowable time of each task to 2 minutes to both reduce frustration and allow comparison with similar studies in children with congenital hemiplegia.[27,28,56] The JTTHF has been shown to be responsive to change due to an intervention; however there are some difficulties with stability of test-retest performance in the unimpaired limb.[27,28,56,57] There is high inter-rater reliability (ICC=0.82-1.0) for each subtest and test-test reliability with 5 patients and 2 raters (r=0.84-0.85) in an aging adult population.[58] The JTHFT has demonstrated good responsiveness to detect change due to interventions that improve upper limb speed and manipulation.[27]

Secondary outcomes will assess Mitii™ against all dimensions of the ICF:

Body Structure and Function domain

a) Executive Functioning

Executive functioning will be assessed across four domains: attentional control, information processing, cognitive flexibility, and attentional control in accordance with Anderson's paediatric model of executive functioning.[59] A neuropsychological test battery will be utilised to assess these domains comprising of subtests from the Delis-Kaplan Executive Function System (D-KEFS)[60] and the Wechsler Intelligence Scale for Children Fourth Edition (WISC-IV).[35] Behavioural manifestations of executive functioning in everyday life will also be assessed using the Behaviour Rating Inventory of Executive Function (BRIEF).[61] All scores will be converted into scaled scores according to normative data based on the child's age and gender.

i) Colour-Word Interference Test (from the D-KEFS)

The Inhibition condition from the Colour-Word Interference Test will be used to measure attentional control. Children will be required to name the ink colour that colour words are printed in across five rows (e.g., say "red" for the word "blue" printed in red ink). The total time (seconds) taken to complete the task will be the primary outcome measure, with longer time indicative of poorer attentional control. Raw scores will be converted into scaled scores (mean=10, SD=3). Excellent test-retest reliability has been shown for the Colour-Word Interference Test (r= 0.90).[62]

ii) Trail Making Test (from the D-KEFS)

The Number Sequencing condition from the Trail Making Test will be used to measure attentional control and the Number-Letter Switching condition will be used to measure cognitive flexibility. In Number Sequencing, children will connect numbers printed on an A3 sheet in numerical order from 1 – 16, while in Number-Letter Switching, children will be required to switch back and forth between connecting numbers in numerical order and letters in alphabetical order, also printed on an A3 sheet, from 1 – 16 and A – P (e.g., "1-a-2-b-3-c"). The total time (seconds) taken to complete each task will be recorded, with a longer time indicating greater difficulty with attention control or cognitive flexibility. Raw scores will be converted into scaled scores (mean=10, SD=3). Adequate test-retest reliability for Number Sequencing (r= 0.77) and Number-Letter Switching (r=0.20-0.55) has been documented.[62]

iii) Tower Test (from the D-KEFS)

The Tower Test will be used to measure goal setting. Children will move five disks across three pegs to build a target tower as illustrated in a picture within a specified time limit. They will be instructed to use the least number of moves possible to complete the tower, that they can only move one disk at a time and that they must never place a larger disk on top of a smaller disk. The total achievement score, which is based on the total number of moves needed to build the tower, and the total number of rule violations will be used to measure goal setting abilities. The lower the achievement score and the higher the rule violations score indicate greater goal setting difficulties. Raw scores will be converted into scaled scores (mean=10, SD= 3). The Tower Test has a moderate to high level of internal consistency (α=0.43-0.84) and adequate test-retest reliability (r= 0.51).[62]

iv) Digit Span (from the WISC-IV)

Digit Span Backwards is a verbal working memory task that requires children to temporarily store and manipulate information and will be used as a measure of cognitive flexibility. A string of numbers will be given verbally to the children increasing from two digits to eight, and they have to repeat the number string in the reverse order (e.g. if "3-7-2" the child should say "2-7-3"). A score of one is given to each string correctly repeated in reverse order with a lower overall score indicating poorer cognitive flexibility. Raw scores will be converted into scaled scores (mean=10, SD=3). Digit Span Backwards has been shown to have a good internal consistency (α=0.80) and adequate test-retest reliability (r=0.74).[63]

v) Coding (from the WISC-IV)

Coding will be used as a measure of information processing. Children will have to copy simple geometric shapes that are paired with numbers within two minutes. The overall number of correctly copied geometric shapes will be calculated, with a lower number indicating poorer information processing. Raw scores will be converted into scaled scores (mean=10, SD=3). Good internal consistency (α=0.82) and test-retest reliability (r=0.81) for Coding has been shown.[63]

vi) Symbol Search (from the WISC-IV)

Information processing will also be assessed using Symbol Search. Children will visually scan for a target symbols in groups of five symbols and indicate whether the target symbol is in the group by placing a line through the word 'yes' or 'no'. Children will be told to work as fast as they can in two minutes. The total number of correctly identified symbols minus the total number of incorrectly identified symbols will be calculated, with lower scores indicating poorer information processing. Raw scores will be converted into scaled scores (mean=10, SD=3). Symbol search has been documented to have an adequate internal consistency (α=0.79) and a high level of test-retest reliability (r=0.80).[63]

vii) Brief Rating Inventory of Executive Function (BRIEF)

In addition to cognitive measures of executive functioning, behavioural manifestations of executive functions in everyday life will be measured using the BRIEF, an 85 item parent-rated questionnaire. Parents rate items (e.g. "does not think before doing") on a three-point scale ranging from 1 (*never*) to 3 (*often*). Two index scores will be obtained from the BRIEF: (1) the behavioural regulation index (BRI), which is derived from four subscales: initiate, working memory, plan, organisation of materials and monitor, and; (2) the metacognition index (MCI), which is derived from three subscales: inhibit, shift, and emotional control. The BRI and MCI will then be combined to form an overall global executive composite score (GEC). Raw scores will be converted into *T* scores (mean=50, SD=10), with higher *T* scores indicating a greater level of executive dysfunction. A *T* score of 65 and above, which is 1.5 standard deviations above the mean, will be used as the cut-off for abnormal elevations across all scales.[61] The BRIEF has been found to be ecologically valid measure of executive functioning and has been shown to have good internal consistency (α=0.80 – 0.98) and high test-retest reliability on the BRI (r= 0.92), MCI (r=0.88), and the GEC (r=0.86).[61]

b) Test of Visual Perceptual Skills (TVPS)

The TVPS-3 is comprised of seven subscales: visual discrimination, visual memory, visual spatial relationships, form constancy, visual sequential memory, figure-ground, and visual closure.[64] Performance will be determined by the number of correct answers in each test (maximally 16 in each of 7 tests). Performance will be scaled according to normative data and converted into a percentage score for the age group. The TVPS-3 is a reliable and valid measure of visual perception in persons aged 4 to 18 years.[64]

c) The Melbourne Assessment of Unilateral Upper Limb Function (MUUL)

The MUUL measures both upper limb impairment and quality of upper limb function.[65] It is designed for children aged 5 to 15 years with CP and consists of sixteen criterion-referenced items measuring aspects of reach, grasp, release, and manipulation. The maximum possible raw score is 122, with raw scores being computed into percentage scores. Inter-rater and intra-rater reliability for the MUUL is very high for total test scores (ICC=0.95 and 0.97, respectively) and moderate to high for individual items (ICC=0.69 – 0.91).[66] The MUUL also has good internal consistency (α=0.96).[66] Construct and content validity for the MUUL was established during test development.[66]

d) Lower Limb Functional Strength

Mitii™ will focus on training functional strength therefore assessment of Repetition Maximum (RM) during functional exercise will be used to assess strength. Functional strength will be tested according to the protocol outline by Verschuren et al.[67]

i) Lateral step-up

This is the number of step up repetitions onto a bench during 30 seconds. This is tested with the stool height adjusted to the GMFCS level (I,II=15-20 cm stool). The child stands with the leg being tested on the stool and the non-testing leg on the floor, with feet parallel and shoulder width apart. The child then extends the test leg (on the stool) to within 10˚ of full knee extension, so that the non-test leg is off the ground, then lowers the foot back down to the floor until either the toes or heel touches.[68] This is considered one full cycle. The child should maintain dorsiflexion of the non-test foot and a horizontal pelvis throughout by keeping hands on hips throughout the test. This is repeated and the number completed within 30 seconds is recorded commencing with the right leg for all children. This is then repeated for the left leg.

ii) Sit-to-stand

This tests the number of sit-to-stand repetitions that can be achieved within 30 seconds, with sit-stand-sit considered a full cycle. The seated position is reached when the knees and hips are in 90˚flexion. Full standing is considered within 15˚ full extensions of the hips and legs. The sit-to-stand must be achieved with arms free and without any support from the chair or the child's body.

iii) Half kneel to stand

This is the number of repetitions of half kneel to stand that can be completed in 30 seconds. The child is positioned in half-kneeling on a mat, with the buttocks clear of the lower leg and/or the floor. The child must then assume a standing position without using the arms or any external support, such as the floor or furniture. Repetitions are counted each time the participant achieves a standing position where both legs and hips are within 15˚ of full extension. This is recorded commencing with the right leg in front, and then repeated with the left leg in front.

For all tests, children will be given 2 practice repetitions per extremity prior to formal testing. Between each practice and testing, 30 seconds rest will be provided. Between tests 180 seconds (3 minutes) rest will be provided. The tests will be assessed in the above order: Lateral step test right, lateral step test left, sit to stand, half kneel to stand right, half kneel to stand left. Children will be instructed to perform as many repetitions as possible in 30 seconds and will be verbally encouraged.

Acceptable inter-tester reliability has been demonstrated for functional strength testing in 25 children with CP ((ICC>0.91; Coefficient of variation (CV)=12.1-22.7%) . Reliability for the tests were strong (Lateral step up ICC=0.94; Sit to stand ICC=0.91; Half kneel to stand ICC=0.93 to 0.96). Mean repetitions for the lateral step up were 13.2 (SD=10.5; standard error of measurement (SEM)=2.4 reps; CV=17.8%) for

the left side, and 12.6 (SD=10.4; SEM=2.6 reps; CV=22.7%) for the right side. Mean number of repetitions for the sit to stand was 14.4 (SD=5.0; SEM=2.6 reps; CV=22.7%). Half kneel to stand was less, with an average of 7.5 reps (SD=5.5; SEM=1.1 reps; CV=28.6%) for the left side and 6.0 (SD=5.3; SEM=1.4 reps; CV=39.9%) for the right side.[67]

e) Six Minute Walk Test (6MWT)

The 6MWT is a simple, sub-maximal clinical exercise test which measures the distance walked (6MWD) under controlled conditions over six minutes. The 6MWT has been found to be reliable in independently ambulant adolescents with CP.[69] In this population, test-retest reliability was excellent (ICC=0.98). Percentile curves for the 6MWT have been created, though these were from 1,445 typically developing Chinese children aged 7-16 years.[70] No reference curves for children and adolescents with CP exist. While children with CP may exhibit lower 6MWD compared to typically developing children due to muscle spasticity, aberrant gait patterns and functional restrictions, GMFCS Levels I and II are able to walk with little to no restrictions therefore one could expect similar test results to a typically developing child. The 6MWT will be performed using standardized verbal encouragement asking the children to walk as fast as possible along a flat, straight, 10m corridor with cones marking the turn-around at each end as per Maher et al.[69]

f) Passive Range of Motion

Upper and lower limb passive range of motion for the unimpaired and impaired side will be assessed by occupational and physiotherapists at baseline.

Activity domain

a) Habitual Physical Activity (HPA)

HPA will be measured using ActiGraph® GT3X+ tri-axial accelerometer (Pensacola, FL). This detects accelerations of a magnitude and frequency with raw acceleration data, proportional to the amount of HPA done by an individual. ActiGraph® units will be fitted during assessment and worn during waking hours for 4 days. After 4 days it will be returned by registered post for data extraction and analysis. An activity diary will be coupled with an ActiGraph® to detect and log accelerations of human movement. Data will be considered for analysis where accelerations are recorded for >4 hrs per day. Analysis will convert counts to activity intensity using Evenson cut points[71] to allow comparison to the national physical activity guidelines.[21,22] The ActiGraph® will also be set up to detect step counts.

The ActiGraph® is a valid instrument to detect HPA in children and adolescents with CP. The ActiGraph® accelerometer is strongly correlated to direct observation during structured activity and free play, and more accurate than heart rate.[72] It has also demonstrated excellent classification accuracy, and

Evenson cut points were found to be the most accurate for adolescents with CP.[73] In typically developing children, the reliability of accelerometers has been shown to increase with increased recording days (ICC: 0.45 for 1 days to 0.9 for 8 days).[74] Seasonal variation has been demonstrated with less activity being performed in the winter months (ICC=0.54).[74] Age has also been found to influence reliability, with typically developing primary school aged children participating in more moderate to vigorous physical activity on weekends and exhibiting less day-to-day variability in activity, requiring only 4-5 days monitoring, in contrast to adolescents who exercise less on weekends and require 8 or 9 days of monitoring.[75] Acceptable reliability has been found with 4 days of monitoring (r=0.75-0.78).[76] However, there is no evidence that documents the reliability of the ActiGraph® in children with CP. Children in the present study will be fitted with an ActiGraph® accelerometer to collect 4 days of free living activity after the assessments and training days. Additionally, further work on the reliability of the ActiGraph® in children and adolescents with CP will be conducted. Participants will rest for a 5 minute period and then conduct selected light, moderate and vigorous assessment tasks, interspersed with 5 minute rest periods in a standardized manner whilst wearing an ActiGraph® monitor and concurrently measuring heart rate and classifying the activity using direct observation. All participants will have the option to undergo this assessment during the assessment and Mitii™ training 2 day visit.

b) Mobility Questionnaire (MobQues)

The MobQues measures mobility of children with CP by assessing amount of difficulty the children have in executing mobility activities. It addresses mobility limitations a child experiences in everyday life and covers a range of severity levels. The MobQues focuses on 47 mobility activities, from which the MobQues47 and the MobQues28 scores can be calculated by scoring 47 or 28 mobility activities, respectively. Response options of the MobQues are: Impossible without help (score 0), very difficult (score 1), somewhat difficult (score 2), slightly difficult (score 3), not difficult at all (score 4).Total scores are calculated by adding all item scores (range 0–4) divided by the maximum possible score and multiplied by 100 to obtain scores on a scale of 0 to 100 (with a low score representing severe limitations in mobility):MobQues47=(Σ item / 188)·100; MobQues28=(Σ item / 112)·100. For research purposes, the shorter version (MobQues28) is recommended due to better measurement properties, whereas the MobQues47 can be used for clinical applications. Content validity of the instrument has been demonstrated as 46 of the 47 test questions relate to the 'mobility' according to the definitions of the ICF. Construct validity was demonstrated as MobQues scores decreased with increasing GMFCS level ($p<0.001$). In a subgroup of 162 children, MobQues score was positively correlated to GMFM-66 (MobQues47, r=0.75; MobQues28, r=0.67, $p<0.001$).[77] It has also been demonstrated to be a reliable instrument.[78] For the strong inter-rater reliability was found for theMobQues47 (ICC=0.92) and MobQues28 (ICC=0.87). The SEM was 7.8 and 8.9 respectively. As expected, the intra-rater reliability was higher for both MobQues versions (ICC=0.96–0.99; SEM=3.5–4.9).[78] The English version has not yet been cross-validated therefore the results

demonstrated may differ slightly to that in an English speaking population. Data sharing has been arranged with the MobQues authors to enable cross cultural validation of this tool. To allow this the MobQues47 clinical version will be used at baseline to obtain a full dataset, and then the MobQues28 will be collected at subsequent assessments. The MobQues28 will be extracted from the baseline assessment to allow comparison across time points.

Participation domain

a) Canadian Occupational Performance Measure (COPM)

Individualised goals will be measured using the COPM to evaluate self-perception of occupational performance over time.[79, 80] The COPM will be administered by one OT with the child/adolescent and parent. The COPM is a standardised individualised, client centred measure that evaluates client's self-perception of occupational performance. Clients identify areas of difficulty in everyday occupational performance and rate their performance and satisfaction for each problem on a scale from 1 to 10. An average score for performance and satisfaction is calculated.[67] The COPM was designed for all ages and disability groups. There is good evidence of construct, content and criterion validity. The retest reliability of the performance and satisfaction scores on the COPM is high (ICC=0.76-0.89).[80-82] The COPM has demonstrated responsiveness to change in paediatric clinical trials,[83, 84] and a 2 point change on COPM performance has been reported as being clinically significant.[79]

b) Assessment of Life Habits (LIFE-H)

The LIFE-H is designed for children aged 5 to 13 years and measures life habits in home, school and neighbourhood environments.[85, 86] It is a questionnaire completed by the parent/caregiver about the child. The child form is based on an adult version. The long form consists of 197 items divided into 12 categories and includes regular activities (e.g. eating meals, communication, and mobility) and social roles. A weighted score ranging from 0 to 10 is generated for each category and overall total.

Evidence of construct validity and criterion validity, with strong correlations between the LIFE-H and PEDI and Functional Independence Measure for Children (WeeFIM), are established.[85, 87] Adequate to excellent internal consistency (α=0.73–0.90 for categories, 0.97 for daily activities and 0.90 for social roles), intra-rater (ICC=0.83–0.95 for daily activities), inter-rater (ICC=0.8–0.91 for daily activities and ICC=0.63–0.9 for social roles) and test-retest reliability (ICC=0.73 for total score) have also been established.[88] Four categories will be evaluated in this study including nutrition (e.g. mealtime activities), personal care (e.g. dressing), education and recreation. These areas were considered to reflect many of the identified difficulties confronted by children with congenital hemiplegia that might be amenable to the intervention program.

c) Participation and Environment Measure for Children and Youth (PEM-CY)

The PEM-CY is a newly developed, parent-report measure for children aged 5 to 17 years that examines participation and environment across three settings: home, school, and community.[89] No interview is required for administration with parents completing the assessment either online or using a paper based form, which supports its use in this large-scale study. The PEM-CY examines the extent to which young people participate in important activity areas within the home, school and community environments, and the extent to which particular features of these environments are perceived to support or challenge the young person's participation. Evidence of the psychometric properties of this new instrument are limited to date, however data from a sample of 576 young people showed internal consistency was moderate to good (□>0.59) across the scales. Test-retest reliability was moderate to good (ICC>0.58) across a 1-4 week period using the online version of the assessment.[90] The PEM-CY will be collected at baseline.

d) Strengths and Difficulties Questionnaire (SDQ)

The SDQ will be used to measure parents' perceptions of prosocial and difficult behaviours in their child.[91, 92] The SDQ has a total of 33 items. The first 25 items are divided into 5 scales and assess the frequency of emotional symptoms, conduct problems, inattention/hyperactivity, peer problems and prosocial behaviour (e.g. "considerate of other people's feelings"). These items are rated upon reflection of the last six months on a three-point scale, from zero (*not true*) to two (*certainly true*). A total score for each scale (0-10) and an overall total difficulties score (0-40) will be calculated, with higher scores indicating more distress on all scales except prosocial behaviour. A clinical cut-off of ≥17 will be utilised on the total difficulties score. The total score on the 5 scales and the overall total difficulties score will be utilised as measures of the child's psychological functioning. Moderate to high internal consistency (α=0.73-0.82) and test-retest reliability (*r* =0.77–0.85) has been shown on the overall total difficulties score.[93, 94]

Cerebral Palsy Quality of Life (CPQOL)

QOL will be measured using a condition specific measure, either the CPQOL-Child parent report[95], or for children 9 years or age or older, the CPQOL-Teen.[96] Results of factor analysis demonstrated that the CPQOL measures 7 broad domains of quality of life: social wellbeing and acceptance, functioning, participation, physical health, emotional wellbeing, access to services, pain, impact of disability and family health. The psychometric properties of the CPQOL-Child are excellent, with strong internal consistency (□=0.74-0.92 for parent-proxy report; □=0.80-0.90 for child self-report). Test re-test is adequate (ICC=0.76-0.89) and it is moderately correlated with generic QOL and health (r=0.30-0.51).[97, 98] The CPQOL-Teen, for adolescents aged 13-18 years has strong psychometric properties, with strong internal consistency (□=0.81-0.95 for the primary caregiver report; □=0.84-0.96 for the adolescent self-report) and strong test re-test reliability for adolescents (ICC=0.84-0.87) and for primary caregivers (ICC=0.72-0.92). In terms of validity, all domains of the CPQOL-Teen parent report (r=0.40-46) and adolescent report (r=0.58-

0.68) were correlated with a generic QOL instrument.[99]

Environmental and Personal Factors

A study questionnaire was developed to capture demographic information that has been shown in the literature to influence a child's participation. These include family ethnicity, household income, parental education and employment, family structure and supports, and family interests. This will be collected at baseline assessments then any changes measured at subsequent assessments. A measure of social advantage/disadvantage will be derived from postcode of residence using the Index of Relative Socio-economic Advantage/Disadvantage from the Australian Bureau of Statistics.[100] Deciles will be reported on a continuum with lower scores reflecting greater socio-economic disadvantage and higher scores reflecting socio-economic advantage.

Economic Analysis

An economic analysis will be conducted to synthesise health outcomes and costs to both families and health systems. Costs will be obtained for healthcare use (measured through self/proxy reports) and measured directly for the intervention (including the number and duration of visits by the intervention team). Standard costs will be assigned to the resource use (e.g. medical care, allied health visits and diagnostic/investigational services will be assigned a cost according to a fee schedule and medications will be costed based on their description, dosage regimens, and whether or not they are listed on the Pharmaceutical Benefits Schedule). Outcomes will be measured as change in Quality of life from baseline to end of intervention based on the CP-QoL. The base case model timeframe will be 20 weeks consistent with the trial follow up and all costs and outcomes will be extrapolated for at least 10 years, with an annual discount rate of 5% applied to both costs and outcomes, to estimate future expected costs and benefits. Sensitivity analyses will be undertaken around key parameters to assess the effect on results from varying these parameters. These can then be compared with other healthcare interventions and value for money judgments made by policy makers. An incremental cost-effectiveness ratio (i.e. $[cost_{MiiTii} - cost_{usual\ care}]/[outcome_{MiiTii} - outcome_{usual\ care}]$ will be calculated.

Statistical analysis

Analysis will follow standard principles for RCTs, using two-group comparisons on all participants on an intention-to-treat basis. External and internal validity of results will be checked using baseline and general descriptive information available for all eligible families; comparing the characteristics of families who completed the study with those who enrolled in the study but did not complete, and those who did not

enrol. Data from each outcome measure will be summarised for each treatment group and descriptive statistics (frequencies, means, medians, 95% CIs) calculated depending on data distribution. The primary comparison immediately post intervention (20 weeks) will be the AMPS and AHA scores. Outcomes between treatment groups will be compared at follow-up using generalised estimating equations (GEEs), with time (0, 20, 40 weeks) and study group (Mitii™, usual care), as well as a time by group interaction as covariables. We will use the Gaussian family, identity link, and an exchangeable correlation structure. Secondary analyses will compare the outcomes between groups for participation (domains of LIFE-H) and QOL (domains of CP-QOL). For dichotomous outcomes we will compare outcomes between-group outcomes using GEEs with the logistic family and logit link. For continuous variables we shall compare using the Gaussian family and identity link (possibly after transformation, depending on the distribution). The magnitude of BOLD changes between groups will be determined using *iBrain*™: ROI will be delineated for each individual primary motor cortex (PM1), SMA, and ipsilateral motor cortex (PM1ipsi) and active voxels in those regions will be counted. These data will be compared for each region over time using GEEs. In subjects where mirror movements did not occur, lateralisation between ipsi- and contralateral PM1 will be assessed to determine the incidence and magnitude of brain reorganisation. For TMS data changes in mean MT to TMS from ipsi and contralateral hemispheres will be analysed in each group at each F/U. The probability of ipsilateral projections appearing as a result of each treatment paradigm will also be analysed. Statistical significance will be at $p<0.05$ with adjustment for multiple comparisons, and all analyses will be intention to treat. Sensitivity analyses using imputation techniques will investigate whether the effect estimates are biased as a consequence of non-ignorable missing data.

DISCUSSION:

Current models of rehabilitation for children with CP are costly, limited by inequity of access and often not provided at sufficient intensity to drive neuroplasticity to improve outcomes. An effective web based multi-modal training that enhances motor and cognitive abilities using virtual trainers is likely to be a cost effective means of delivering therapy. It is also likely to lead to better translation of skills into the community as participants are responsible for their own training in the home environment. This study has the potential to establish a new cost-effective evidence-based therapy accessible equally by urban, rural and remote children and their families. Should our hypotheses be correct, Mitii™ has the potential to revolutionize delivery of intensive rehabilitation to children and adolescents with CP.

Competing Interests: The authors declare they have no competing interests.

Funding: Project grant: Foundation for Children Grant (RB; JZ), Queensland Government Smart Futures PhD Scholarship (SJ), Smart Futures Co-Investment Program Grant (RB; JZ, AS, SR, TC, PS); NHMRC Career Development Fellowship (RB, 1037220), NHMRC TRIP Fellowship (LS, 1036183), APA Scholarship (LM). The funding bodies have not and will not contribute to the study design; the collection,

management, analysis and interpretation of data; the writing of the final reports or the decision to submit findings for publications.

Authors Contributions: RB, JZ, LS, AS and SR are the chief investigators (CIs) who designed and established this research study. The content of the therapy program Mitii™ was developed by the Helene Elsass Centre then adapted and modified in English for the Australian study. LM drafted the first version of this manuscript. All authors have contributed to the writing of the manuscript and have critically reviewed and approved the final version. RB, JZ and LM were responsible for ethics applications and reporting. SR, RC and RB were responsible for the design, implementation, data collection, analysis of the Advanced Brain Imaging studies. RB, JZ, LS, KW, LM and SJ will take lead roles on data management and preparation of publications on the clinical outcomes of the study and RB, SR, RC will take lead roles on the neuroscience publications from the study. TC and PS will lead the economic evaluation and associated publications. KW advised on EF assessments and will advise on their interpretation. QCPRRC is responsible for the coordination, delivery, ethics, outcomes and study publication. The CI's oversee scientific conduct of the trial.

Acknowledgements: Thank you to the staff from the Helene Elsass Centre and The University of Copenhagen who have provided the Mitii™ program, advised on the Mitii™ content and have provided ongoing support to the Mitii™ training.

REFERENCES

1. Rosenbaum P, Paneth N, Leviton A, et al. A report: the definition and classification of cerebral palsy April 2006. *Dev Med Child Neurol Suppl* 2007;**109**:8-14.
2. Odding E, Roebroeck ME, Stam HJ. The epidemiology of cerebral palsy: incidence, impairments and risk factors. *Disabil Rehabil* 2006;**28**:183-91.
3. Access Economics. The Econonic Impact of Cerebral Palsy in Australia in 2007. Canberra, ACT: Access Economics, 2008.
4. Boyd R, Sakzewski L, Ziviani J, et al. INCITE: A randomised trial comparing constraint induced movement therapy and bimanual training in children with congenital hemiplegia. *BMC Neurol* 2010;**10**:4.
5. 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.
6. Sakzewski L, Ziviani J, Abbott DF, et al. Participation outcomes in a randomized trial of 2 models of upper-limb rehabilitation for children with congenital hemiplegia. *Arch Phys Med Rehabil* 2011;**92**:531-9.
7. Boyd R, Abbott D, Badawi N, et al. Use-dependant neuroplasticity in an RCT of constraint induced movement therapy versus bimanual training for children with congenital hemiplegia [abstract]. *Dev Med Child Neurol* 2010;**52**(Suppl 5):11.
8. Foley L, Maddison R. Use of active video games to increase physical activity in children: a (virtual) reality? *Pediatr Exerc Sci* 2010;**22**:7-20.
9. Maher CA, Williams MT, Olds T, et al. Physical and sedentary activity in adolescents with cerebral palsy. *Dev Med Child Neurol* 2007;**49**:450-7.
10. Zwier JN, van Schie PEM, Becher JG, et al. Physical activity in young children with cerebral palsy. *Disabil Rehabil* 2010;**32**:1501-08.
11. Nelson MC, Neumark-Stzainer D, Hannan PJ, et al. Longitudinal and secular trends in physical activity and sedentary behavior during adolescence. *Pediatrics* 2006;**118**:e1627-34.
12. WHO. Health and Development through Physical Activity and Sport. Geneva: WHO, 2003.
13. WHO. International Classification of Functioning, Disability and Health. Geneva, Switzerland: WHO, 2001.
14. Christiansen C, Baum C, Editors. Occupational Therapy – Overcoming Human Performance Deficits. New Jersey: Slack Incorporated, 1991.
15. Van Zelst BR, Miller MD, Russo RN, et al. Activities of daily living in children with hemiplegic cerebral palsy: a cross-sectional evaluation using the Assessment of Motor and Process Skills. *Dev Med Child Neurol* 2006;**48**:723-7.
16. Cusick A, McIntyre S, Novak I, et al. A comparison of goal attainment scaling and the Canadian Occupational Performance Measure for paediatric rehabilitation research. *Pediatr Rehabil* 2006;**9**:149-57.
17. Krebs HI, Fasoli SE, Dipietro L, et al. Motor Learning Characterizes Habilitation of Children With Hemiplegic Cerebral Palsy. *Neurorehabil Neural Repair* 2012
18. Chan RCK, Shum D, Toulopoulou T, et al. Assessment of executive functions: Review of instruments and identification of critical issues. *Arch Clin Neuropsychol* 2008;**23**:201-16.
19. Bodimeade H, Whittingham K, Lloyd O, et al. Executive function in children and adolescents with the congential hemiplegia type of cerebral palsy [Doctor of Psychology]. The University of Queensland, 2011.
20. Bilde PE, Kliim-Due M, Rasmussen B, et al. Individualized, home-based interactive training of cerebral palsy children delivered through the Internet. *BMC Neurol* 2011;**11**:32.
21. Department of Health and Ageing. Australia's Physical Activity Recommendations for 5-12 year olds. Canberra, 2004.
22. Department of Health and Ageing. Australia's Physical Activity Recommendations for 12-18 year olds. Canberra, 2004.
23. Palisano R, Rosenbaum P, Walter S, et al. Development and reliability of a system to classify gross motor function in children with cerebral palsy. *Dev Med Child Neurol* 1997;**39**:214-23.
24. Eliasson AC, Krumlinde-Sundholm L, Rosblad 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.
25. Badawi N, Watson L, Petterson B, et al. What constitutes cerebral palsy? *Dev Med Child Neurol* 1998;**40**:520-7.
26. Loubinoux I, Carel C, Alary F, et al. Within-session and between-session reproducibility of cerebral sensorimotor activation: a test-retest effect evidenced with functional magnetic resonance imaging. *J Cereb Blood Flow Metab* 2001;**21**:592-607.
27. Charles JR, Wolf SL, Schneider JA, et al. Efficacy of a child-friendly form of constraint-induced movement therapy in hemiplegic cerebral palsy: a randomized control trial. *Dev Med Child Neurol* 2006;**48**:635-42.
28. Gordon AM, Schneider JA, Chinnan A, et al. Efficacy of a hand-arm bimanual intensive therapy (HABIT) in children with hemiplegic cerebral palsy: a randomized control trial. *Dev Med Child Neurol* 2007;**49**:830-38.
29. Krageloh-Mann I, Horber V. The role of magnetic resonance imaging in elucidating the pathogenesis of cerebral palsy: a systematic review. *Dev Med Child Neurol* 2007;**49**:144-51.
30. Guzzetta A, Sinclair K, Clarke D, et al. A novel semi-quantitative scale for classification of brain MRI for children with cerebral palsy [abstract]. *Dev Med Child Neurol* 2010;**52**(Suppl 5):74.

31. Palisano RJ, Hanna SE, Rosenbaum PL, et al. Validation of a model of gross motor function for children with cerebral palsy. *Physical Therapy* 2000;**80**:974-85.
32. Morris C, Galuppi BE, Rosenbaum PL. Reliability of family report for the gross motor function classification system. *Dev Med Child Neurol* 2004;**46**:455-60.
33. Morris C, Kurinczuk JJ, Fitzpatrick R, et al. Reliability of the manual ability classification system for children with cerebral palsy. *Dev Med Child Neurol* 2006;**48**:950-53.
34. Crawford JR, Anderson A, Rankin PM, et al. An index-based short-form of the WISC-IV with accompanying analysis of the reliability and abnormality of differences. *Br J Clin Psychol* 2010;**49**:235-58.
35. Wechsler D. Wechsler Intelligence Scale for Children - fourth edition: administration and scoring manual. New York: Psychological Corporation 2004.
36. Lehericy S, Bardinet E, Tremblay L, et al. Motor control in basal ganglia circuits using fMRI and brain atlas approaches. *Cereb cortex* 2006;**16**:149-61.
37. Waites A, Stanislavsky A, Abbott D, et al. The effect of prior cognitive state on resting state networks measured with functional connectivity. *Hum Brain Mapp* 2005;**24**:59-68.
38. Abbott D, Jackson G. iBrain((R)) - Software for analysis and visualisation of functional MR images. *Neuroimage* 2001;**13**:S59-S59.
39. Frackowiak R, Friston K, Frith C, et al. Human Brain Function. 2nd ed. San Diego: Academic Press, 2003.
40. Tournier JD, Calamante F, Connelly A. Robust determination of the fibre orientation distribution in diffusion MRI: Non-negativity constrained super-resolved spherical deconvolution. *Neuroimage* 2007;**35**:1459-72.
41. Tournier JD, Calamante F, Connelly A. MRtrix: Diffusion tractography in crossing fiber regions. *Int J Imaging Syst Technol* 2012;**22**:53-56.
42. Rose S, Guzzetta A, Pannek K, et al. MRI structural connectivity, disruption of primary sensorimotor pathways, and hand function in cerebral palsy. *Brain Connect* 2011;**1**:309-31.
43. Raffelt D, Tournier JD, Rose S, et al. Apparent Fibre Density: a novel measure for the analysis of diffusion-weighted magnetic resonance images. *Neuroimage* 2012;**59**:3976-399.
44. Rose S, Pannek K, Bell C, et al. Direct evidence of intra- and interhemispheric corticomotor network degeneration in amyotrophic lateral sclerosis: an automated MRI structural connectivity study. *Neuroimage* 2012;**59**:2661-9.
45. Rose S, Rowland T, Pannek K, et al. Structural hemispheric asymmetries in the human precentral gyrus hand representation. *Neuroscience* 2012;**210**:211-21.
46. Zalesky A, Fornito A, Bullmore ET. Network-based statistic: identifying differences in brain networks. *Neuroimage* 2010;**53**:1197-207.
47. Rossini PM, Barker AT, Berardelli A, et al. Noninvasive electrical and magnetic stimulation of the brain, spinal-cord and roots - basic principles and procedures for routine clinical-application. Report of an IFCN committee. *Electroencephalogr Clin Neurophysiol* 1994;**91**:79-92.
48. Facchini S, Muellbacher W, Battaglia F, et al. Focal enhancement of motor cortex excitability during motor imagery: a transcranial magnetic stimulation study. *Acta Neurol Scand* 2002;**105**:146-51.
49. Sohn YH, Kaelin-Lang A, Jung HY, et al. Effect of levetiracetam on human corticospinal excitability. *Neurology* 2001;**57**:858-63.
50. Brasil-Neto JP, Cohen LG, Panizza M, et al. Optimal focal transcranial magnetic activation of the human motor cortex: effects of coil orientation, shape of the induced current pulse, and stimulus intensity. *J Clin Neurophysiol* 1992;**9**:132-36.
51. Fisher A, Bray Jones K. Assessment of Motor and Process Skills. Vol. 1. Development, Standardization, and Administration Manual. 7th ed. Forts Collins, CO: Three Star Press, 2010.
52. Krumlinde-Sundholm L, Eliasson A. Development of the Assisting Hand Assessment: a Rasch-built measure intended for children with unilateral upper limb impairments. *Scan J Occup Ther* 2003;**10**:16-26.
53. Holmefur M, Krumlinde-Sundholm L, Eliasson A. Interrater and intrarater reliability of the assisting hand assessment. *Am J Occup Ther* 2007;**61**:79-84.
54. Holmefur M, Aarts P, Hoare B, et al. Retest and alternate forms reliability of the Assisting Hand Assessment [PhD Thesis]. Karolinska Institutet, 2009.
55. Taylor N, Sand PL, Jebsen RH. Evaluation of hand function in children. *Arch Phys Med Rehabil* 1973;**54**:129-35.
56. Eliasson A, Shaw K, Ponten E, et al. Feasibility of a day-camp model of modified constraint induced movement therapy with and without Botulinum Toxin A injections for children with hemiplegia. *Phys Occup Ther Pediatr* 2009;**29**:311-33.
57. Eliasson AC, Krumlinde-Sundholm L, Shaw K, et al. Effects of constraint-induced movement therapy in young children with hemiplegic cerebral palsy: an adapted model. *Dev Med Child Neurol* 2005;**47**:266-75.
58. Hackel ME, Wolfe GA, Bang SM, et al. Changes in hand function in the aging adult as determined by the Jebsen Test of Hand Function. *Phys Ther* 1992;**72**:373-7.
59. Anderson P. Assessment and development of executive function (EF) during childhood. *Child Neuropsychol* 2002;**8**:71-82.

60. Delis DC, Kaplan E, Kramer JH. Delis-Kaplan Executive Function System (D-KEFS) examiner's manual. San Antonio, TX: The Psychological Corporation. 2001.
61. Gioia G, Isquith P, Guy S, et al. Behavior Rating Inventory of Executive Function. Odessa, FL: Psychological Assessment Resources, 2000.
62. Delis DC, Kaplan E, Kramer JH. Delis-Kaplan Executive Function System (D-KEFS) technical manual. San Antonio, Tx: The Psychological Corporation, 2001.
63. Wechsler D. Wechsler Intelligence Scale for Children - fourth edition: technical and interpretative manual. San Antonio, TX: The Psychological Corporation, 2003.
64. Martin NA. Test of Visual Perceptual Skills. 3rd ed. Novato, CA.: Academic Therapy Publications, 2006.
65. Randall M, Johnson L, Reddihough D. The Melbourne Assessment of Unilateral Upper Limb Function Test: Test administration manual. Melbourne: Royal Children's Hospital, 1999.
66. Randall M, Carlin JB, Chondros P, et al. Reliability of the melbourne assessment of unilateral upper limb function. *Dev Med Child Neurol* 2001;**43**:761-67.
67. Verschuren O, Ketelaar M, Takken T, et al. Reliability of hand-held dynamometry and functional strength tests for the lower extremity in children with Cerebral Palsy. *Disabil Rehabil* 2008;**30**:1358-66.
68. Worrell TW, Borchert B, Erner K, et al. Effect of a lateral step-up exercise protocol on quadriceps and lower extremity performance. *J Orthop Sports Phys Ther* 1993;**18**:646-53.
69. Maher CA, Williams MT, Olds TS. The six-minute walk test for children with cerebral palsy. *Int J Rehabil Res* 2008;**31**:185-8.
70. Li AM, Yin J, Au JT, et al. Standard reference for the six-minute-walk test in healthy children aged 7 to 16 years. *Am J Respir Crit Care Med* 2007;**176**:174-80.
71. Evenson KR, Catellier DJ, Gill K, et al. Calibration of two objective measures of physical activity for children. *J Sports Sci* 2008;**26**:1557-65.
72. Capio CM, Sit CH, Abernethy B. Physical activity measurement using MTI (actigraph) among children with cerebral palsy. *Arch Phys Med Rehabil* 2010;**91**:1283-90.
73. Clanchy KM, Tweedy SM, Boyd RN, et al. Validity of accelerometry in ambulatory children and adolescents with cerebral palsy. *Eur J Appl Physiol* 2011;**111**:2951-9.
74. De Vries SI, Van Hirtum HWJEM, Bakker I, et al. Validity and reproducibility of motion sensors in youth: A systematic update. *Med Sci Sports Exerc* 2009;**41**:818-27.
75. Trost SG, Pate RR, Freedson PS, et al. Using objective physical activity measures with youth: How many days of monitoring are needed? *Med Sci Sports Exerc* 2000;**32**:426-31.
76. Janz KF. Validation of the CSA accelerometer for assessing children's physical activity. *Med Sci Sports Exerc* 1994;**26**:369-75.
77. van Ravesteyn NT, Scholtes VA, Becher JG, et al. Measuring mobility limitations in children with cerebral palsy: content and construct validity of a mobility questionnaire (MobQues). *Dev Med Child Neurol* 2010;**52**:e229-35.
78. Van Ravesteyn NT, Dallmeijer AJ, Scholtes VA, et al. Measuring mobility limitations in children with cerebral palsy: interrater and intrarater reliability of a mobility questionnaire (MobQues). *Dev Med Child Neurol* 2010;**52**:194-9.
79. Law M, Baptiste S, Carswell A, et al. The Canadian Occupational Performance Measure. 3rd ed. Ottawa, Ontario: COAT Publications ACE, 1999.
80. Law M, Polatajko H, Pollock N, et al. Pilot testing of the Canadian Occupational Performance Measure: clinical and measurement issues. *Can J Occup Ther* 1994;**61**:191-7.
81. Dedding C, Cardol M, Eyssen I, et al. Validity of the Canadian occupational performance measure: a client-centred outcome measurement. *Clin Rehabil* 2004;**18**:660-67.
82. McColl M, Paterson M, Davies D, et al. Validity and community utility of the Canadian Occupational Performance Measure. *Can J Occup Ther* 2000;**67**:22-30.
83. Lowe K, Novak I, Cusick A. Low-dose/high-concentration localized botulinum toxin A improves upper limb movement and function in children with hemiplegic cerebral palsy. *Dev Med Child Neurol* 2006;**48**:170-75.
84. Wallen M, O'Flaherty SJ, Waugh MCA. Functional outcomes of intramuscular botulinum toxin type A and occupational therapy in the upper limbs of children with cerebral palsy: A randomized controlled trial. *Arch Phys Med Rehabil* 2004;**88**:1-10.
85. Fougeyrollas P, Noreau L, Lepage C. Assessment of Life Habits, Children Long Form. Quebec.: RIPPH/INDCP, 2002.
86. Marincek C, Buhler C, Knops H, et al., eds. The LIFE-H: Assessment of the quality of social participation; 2001 2001; Slovenia.
87. Noreau L, Lepage C, Boissiere L, et al. Social participation in children with cerebral palsy: measurment issues and applications. *Dev Med Child Neurol* 2004;**45**:43-44.
88. Noreau L, Lepage C, Boissiere L, et al. Measuring participation in children with disabilities using the assessment of life habits. *Dev Med Child Neurol* 2007;**49**:666-71.

89. Coster W, Law M, Bedell G, et al. Development of the participation and environment measure for children and youth: conceptual basis. *Disabil Rehabil* 2012;**34**:238-46.

90. Coster W, Bedell G, Law M, et al. Psychometric evaluation of the Participation and Environment Measure for Children and Youth. *Dev Med Child Neurol* 2011;**53**:1030-7.

91. Goodman R. The Strengths and Difficulties Questionnaire: A research note. *J Child Psychol Psychiatry* 1997;**38**:581-86.

92. Goodman R. The extended version of the Strengths and Difficulties Questionnaire as a guide to psychiatric caseness and consequent burden. *J Child Psychol Psychiatry* 1999;**40**:791-99.

93. Goodman R. Psychometric propeties of the Strengths and Difficulties Questionnaire. *J Am Acad Child Adolesc Psychiatry* 2001;**40**:1337-45.

94. Hawes DJ, Dadds MR. Australian data and psychometric propeties of the Strengths and Difficulties Questionnaire. *Aust N Z J Psychiatry* 2004;**38**:644-51.

95. Waters E, Davis E, Boyd R, et al. Cerebral Palsy Quality of Life Questionnaire for Children (CP QOL-Child) Manual. Melbourne: Deakin University, 2006.

96. Davis E, Shelly A, Waters E, et al. Quality of life of adolescents with cerebral palsy: perspectives of adolescents and parents. *Dev Med Child Neurol* 2009;**51**:193-9.

97. Davis E, Waters E, Mackinnon A, et al. Paediatric quality of life instruments: a review of the impact of the conceptual framework on outcomes. *Dev Med Child Neurol* 2006;**48**:311-8.

98. Waters E, Davis E, Mackinnon A, et al. Psychometric properties of the quality of life questionnaire for children with CP. *Dev Med Child Neurol* 2007;**49**:49-55.

99. Davis E, Mackinnon A, Davern M, et al. Description and psychometric properties of the CP QOL-Teen: a quality of life questionnaire for adolescents with cerebral palsy. *Res Dev Disabil* 2013;**34**:344-52.

100. Australian Bureau of Statistics. Census of Population and Housing: Socio-economic Indexes for Areas (SEIFA), 2006. Canberra: ABS, 2008.

Table 1. Tasks and domains trained within the Mitii™ program and the corresponding actions, parameters that can be manipulated by therapists and results received for each task (Please note: Content of Mitii™ is copyright to Mitii™ Development A/S)

Task	Task description	Action	Parameters adjusted	Domains trained	Results displayed
Memory	Memorise a sequence of images	Look at number of images. Images disappear and client must memories them in order which they were shown. Displays sample of images and uses upper limb movement to re-create sequence	Number of images displayed Number of images in sequence Length of time displayed Complexity of images Position of images Number of Repetitions	Upper limb movement Memory/cognition Visual perception	% Correct Time spent on exercise
Brick	Ability to recognise the outline of a picture	Sequence of images displayed, one of which matches shape. Client uses upper limb to drag corresponding image to shape	Number of images Rotation of figures Position of images Position of shape Number of repetitions Complexity of images	Upper limb movement Memory/cognition Visual perception	% Correct Time spent on exercise
Figure builder	Ability to construct a complete image from smaller pieces	An image is in the middle of screen. Small pieces of this and other images are falling down either side. Use upper limb to reach and drag corresponding piece to recreate image from bottom to top.	Number of images Number of pieces Interval between pieces Speed of falling pieces Number of repetitions Complexity of images	Upper limb movement Memory/cognition Visual perception	Number of pieces missed Time spent on exercise
Figure ground	Ability to pick out a figure from an unorganised background	Large background image presented. Use upper limb to pick up small brick and drag to corresponding place in image.	Time held over correct place Precision of placement Number of repetitions Complexity of background	Upper limb movement Visual perception	Time spent on exercise
Spatial relation	Ability to perceive spatial orientation of a figure	Use upper limb to touch the image in the sequence which differs. (Eg. Pear, Apple, Orange, Car. The car is different.)	Number of images Interval between images Time held over correct image Number of repetitions Complexity of images	Upper limb movement Visual perception	% Correct Time spent on exercise
Visual Closure	Ability to recognise an incomplete figure	Series of incomplete images displayed, and complete single image. Use upper limb to drag incomplete image to complete image. Correct image is one that if complete, would be identical to the presented complete image.	Number of images Position of images Internal between images Time held over correct image Repetitions Complexity of images	Upper limb movement Visual perception	% Correct Time spent on exercise

Balloon mathematics	Ability to complete mathematical calculations	Equation and a number of answer options are presented in balloons. Use upper limb to drag pin and pop balloon with correct answer.	Complexity of equation Number of terms in equation Size of number in equation Time held over correct balloon Time equation displayed Time answer displayed Position of balloons Position of pin Number of repetitions	Upper limb movement Memory/cognition Visual perception	% Correct Time spent on exercise
Combination (2-hand exercise)	Ability to co-ordinated both upper limbs	Series of images presented on both sides. Use both hands to drag two matching items into a circle in the centre of the screen	Number of images presented Number of matching pairs Location of goal circle Size of goal circle Time held on correct image Time held in goal circle Number of repetitions Time bomb Complexity of images	Bimanual upper limb coordination Memory/cognition Visual Perception Time challenge	% Correct Time spent on exercise
Flight simulator	Ability to balance against series of lateral displacements	Use band on head to steer the plane against a series of lateral wind gust disturbances	Airplane speed Wind direction Time of wind gust Strength of wind gust Exercise duration	Balance	Time spent on exercise Balance distribution
Follow	Ability to control gross motor movements and activate larger muscle groups	Use band on head to steer an object around screen	Route of object Speed of object movement Amplitude of object movement Size of object Number of repetitions	Lower limb strength Balance	Time spent on exercise % Correct route
Get up/Get down	Activate larger muscle groups to increase intensity and pulse rate	Use band on head to steer object from top to bottom of screen while doing gross motor movement (eg. Sit to stand, Squat to stand, Lunge to stand, Step on/off block)	Location of object Number of repetitions Time bomb	Lower limb strength Balance Time challenge	Time spent on exercise Time per repetition
Follow the leader	Follow a sequence of movements	Video sequence uploaded and client follows visualising themselves and the video in a split screen view	Video created by therapist therefore can modify	Lower limb strength Balance	
UFO	Ability to control gross motor movements and activate larger muscle groups	Use band on head to steer UFO through a series of tunnels. Requires client to squat/extend knees to control	Route of object Speed of object movement Number of repetitions Time bomb	Lower limb strength Balance Time challenge	Time spent on exercise Accuracy of object path

Move	Activate larger muscle groups to increase intensity and pulse rate	Uses large movement of limbs to inflate a balloon until it bursts	Amplitude of movements Movement direction Duration of movement Number of repetitions	Time spent on exercise % increase of balloon
Additional demands				
Balance	Put on wobble board, reduce base of support (e.g. standing on one leg)			
Strength	Step on/off block			

Article type: Protocol paper

Title: Move it to improve it (Mitii™): Study protocol of a randomised controlled trial of a novel web-based multi-modal training program for children and adolescents with cerebral palsy

Short title: Mitii™: Randomised controlled trial of a novel web based program for cerebral palsy

Authors:

Roslyn N Boyd [1,2]

Louise E Mitchell [1,2]

Sarah T James [1,2]

Jenny Ziviani [2, 3]

Leanne Sakzewski [1,2]

Anthony Smith[4]

Stephen Rose[5]

Ross Cunnington [6,7]

Koa Whittingham [1,7]

Robert S Ware[8,9]

Tracey A Comans [10]

Paul A Scuffham [10]

[1] Queensland Cerebral Palsy and Rehabilitation Research Centre, School of Medicine, Faculty of Health Sciences, The University of Queensland, Brisbane, Australia
[2] Children's Allied Health Research, Children's Health Queensland, Herston, Brisbane, Australia
[3] School of Health and Rehabilitation Sciences, The University of Queensland, Brisbane, Australia
[4] Centre for Online Health, University of Queensland, Australia
[5] CSIRO, ICT - Australian e-Health Research Centre, Royal Brisbane and Women's Hospital Centre for Clinical Research, The University of Queensland
[6] Queensland Brain Institute, The University of Queensland, Brisbane, Australia
[7]School of Psychology, The University of Queensland
[8] Queensland Children's Medical Research Institute, The University of Queensland
[9] School of Population Health, The University of Queensland;
[10] Griffith Health Institute and School of Medicine, Griffith University, Brisbane, Queensland

Email addresses:

RB:r.boyd@uq.edu.au
LM: louise.mitchell@uq.edu.au
SJ: s.james2@uq.edu.au
JZ:j.ziviani@uq.edu.au
LS: l.sakzewski1@uq.edu.au
AS: asmith@uq.edu.au
SR: Stephen.Rose@csiro.au
RC: r.cunnington@uq.edu.au;
KW: koawhittingham@uq.edu.au
RSW: r.ware@sph.uq.edu.au
TC: t.comans@griffith.edu.au
PS: p.scuffham@griffith.edu.au

Corresponding Author: Professor Roslyn Boyd

Address*:* Queensland Cerebral Palsy and Rehabilitation Research Centre, Level 7, Block 6, Royal Brisbane and Women's Hospital, Herston QLD 4029, Australia.

Key words: Cerebral Palsy, Congenital Hemiplegia, Telerehabilitation, Virtual Reality, Physical Activity, Executive Function, Randomized Trial, Protocol.

Target Journal: BMJ Open

Article Summary

‘Article focus’

- The main aim of this proposed study is to determine if 20 weeks of intensive Mitii™ training can improve upper-limb activity (unimanual and bimanual), occupational performance and cognitive skills in children and adolescents with CP compared to standard care.
- The secondary aim is to further our understanding of the central neurovascular mechanisms underlying changes in UL function, motor planning, and executive function (using functional magnetic resonance imaging (fMRI) and TMS to measure central activation in the parts of the brain controlling movement).
- It is hypothesized that Mitii™ will be more effective than Usual Care (OT/PT) for children with congential hemiplegia (aged 8-18 years) to improve activity (unimanual capacity and bimanual performance) by a mean difference of 5 points on the Assisting Hand Assessment (AHA) and 10% decrease in time on the Jebsen-Taylor Test of Hand Function (JTTHF), and motor and process skills (AMPS) will improve by 0.5 logit scores following Mitii™ intervention.

‘Key messages’

- Persons with cerebral palsy require a lifetime of costly and resource intensive interventions which are often limited by equity of access. With increasing burden being placed on health systems, new methods to deliver intensive rehabilitation therapies are needed.
- Mitii™ is an internet based multi-modal training program comprising upper-limb and cognitive training within the context of meaningful physical activity. This is the first time this new technology will be tested to a randomised trial and it is expected this trial.

‘Strengths and limitations’

- This study uses a strong design methodology, utilising a matched paired, waitlist controlled, single blinded randomised trial
- This study will use outcomes measures across all domains of the International Classification of Functioning, Disability and Health Framework (ICF) to test the efficacy of Mitii™

ABSTRACT:

Introduction: Persons with cerebral palsy require a lifetime of costly and resource intensive interventions which are often limited by equity of access. With increasing burden being placed on health systems, new methods to deliver intensive rehabilitation therapies are needed. Move it to improve it (Mitii™) is an internet based multi-modal program comprising upper-limb and cognitive training with physical activity. It can be accessed in the client's home at their convenience. The proposed study aims to test the efficacy of Mitii™ in improving upper-limb function and motor planning. Additionally, this study hopes to further our understanding of the central neurovascular mechanisms underlying the proposed changes and determine the cost effectiveness of Mitii™.

Methods and analysis: Children with congenital hemiplegia will be recruited to participate in this waitlist control, matched pairs, single blind randomised trial. Children will be matched at baseline and randomly allocated to receive 20 weeks of 30 minutes of daily Mitii™ training immediately, or waitlist for 20 weeks before receiving the same Mitii™ training (potential total dose=70hours). Outcomes will be assessed at 20 weeks after Mitii™ commencement, and retention effects tested at 40 weeks. The primary outcomes will be the Assessment of Motor and Process Skills (AMPS), the Assisting Hand Assessment (AHA), and unimanual upper-limb capacity using the Jebsen Taylor Test of Hand Function (JTTHF). Advanced brain imaging will assess use-dependant neuroplasticity. Measures of body structure and functions, activity, participation and quality of life will be used to assess Mitii™ efficacy across all domains of the International Classification of Functioning, Disability and Health framework.

Ethics and Dissemination: This project has received Ethics Approval from the Medical Ethics Committee of The University of Queensland (2011000608) and the Royal Children's Hospital Brisbane (HREC/11/QRCH/35). Findings will be disseminated widely through conference presentations, seminars and peer-reviewed scientific journals.

Trial Registration: ACTRN12611001174976

BACKGROUND:

Cerebral palsy (CP) describes a group of disorders of the development of movement and posture, causing activity limitations, which are attributed to non-progressive disturbances that occurred in the developing foetal or infant brain. The motor disorders of CP are often accompanied by disturbances of sensation, cognition, perception, behaviour, and/or seizure disorders, and by secondary musculoskeletal problems.[1] In Australia, around 600-700 infants are born with CP each year, making it the most common physical disability in childhood.[2] There remains no cure for CP, meaning that an infant born with this condition will require a lifetime of investigations, interventions and equipment. In 2007, CP was estimated to cost $AUD1.47 billion per annum, equating to a per capita financial burden of AUD$43,431 per person with CP per annum.[3] CP is not only a costly but burdensome condition, impacting the individual, his/her family and society more generally. These impacts highlight the need to optimize health, function and fitness of individuals with CP to reduce costs associated with the condition.

Several intensive therapy approaches delivered by a therapist directly with the child with CP are currently offered to improve upper-limb (UL) function. A systematic review and meta-analysis of all non-surgical upper-limb interventions found some evidence to support these intensive training approaches (e.g. modified Constraint Induced Movement Therapy (mCIMT) and bimanual training (BIM)) to improve the amount of use (effect size [ES]=1.54) and efficiency of movement (ES=0.44) of the impaired arm and new repertoires of hand skills (ES=1.22). Our group recently completed a single blind (evaluator masked) randomized trial (INCITE NHMRC:368500) which directly compared two intensive UL training approaches, mCIMT and BIM to improve unimanual capacity, bimanual performance, societal participation and quality of life.[4] Children attended 60 hours of direct training in groups with either context or method of training over 10 days. In a matched pairs design of 32 pairs of children with congenital hemiplegia (64 children in total) there were minimal differences between the two approaches, both improving activity performance equally in the short term (3wks) with mCIMT yielding greater changes in unimanual capacity at six months.[5,6]

In addition to functional changes children receiving mCIMT had greater and earlier use-dependent neuroplasticity, measured with Transcranial Magnetic Stimulation (TMS) immediately post intervention, than those receiving BIM which was sustained at 6 months.[7] These results suggest that a minimum of 60 hours in a block of training is required to drive neuroplasticity, which has implications for the current dose and intensity of standard training regimens for children with unilateral CP. These findings support the need for training to be intensive, repetitious and incrementally challenging in order to drive neuroplasticity.

The challenge is that while both interventions are effective they are costly and require 60 hours of direct rehabilitation provided by specialist trained occupational therapists (OT) and/or physiotherapists (PT). Implementing direct intensive interventions in specialist settings also potentially limits access to children who live in major metropolitan centres. The reality is that current clinical practice affords children with

unilateral CP only consultative or time-limited therapy following pharmacological intervention (1-12 hours/year). Limited available health resources mean the amount of therapy may be insufficient to drive neuroplastic changes necessary for functional improvements to occur. Alternatives for intensive rehabilitation programs are required. Internet delivered programs and 'active' video games are emerging as a popular modality for paediatric interventions. These systems have the potential to deliver novel, engaging and intensive therapies to children in both metropolitan and more isolated areas where services are limited, in a potentially cost effective manner.

'Active' video games not only have the potential to deliver upper-limb interventions, but also to use otherwise sedentary screen time to promote physical activity. Children today, particularly those with motor disabilities which limit participation in sports or exercise, spend increased time in sedentary screen-based leisure activities, such as watching television or playing sedentary video games. This displaces more active behaviours which in part contributes to obesity and other adverse health outcomes.[8] It is known that children and adolescents with CP are less physically active than their typically developing peers[9, 10], or compared to children with other physical disabilities, such as spina bifida or head injuries.[11] This is an important health promotion consideration as patterns of physical activity acquired during childhood years are more likely to be maintained into adult life, providing the foundation for healthy lifestyle choices.[12] Additionally, for school aged children with CP, interventions including intramuscular Botulinum toxin type-A, casting and surgery usually followed by a limited amount of therapy are common at this age. Success of these interventions should be assessed against all dimensions of the International Classification of Functioning, Disability and Health (ICF)[13], including their impact on physical activity capacity and performance, as well as participation.

Activities of daily living (ADL) (i.e. life tasks required for self-care and self-maintenance) are fundamental in supporting participation across school, home and community environments.[14] Children and adolescents with unilateral CP often experience difficulties with ADL due to their motor and associated difficulties.[15] Performance of ADL tasks is a high priority for parents/guardians.[16] Therapy targeting ADL for children with unilateral CP often involves task specific training to stimulate motor learning.[17] Alternatively, therapy may address deficits in motor and cognitive skills that are considered prerequisites for successful ADL performance. Rehabilitation that involves a combination of upper limb, gross motor, cognitive and visual perceptual training is likely to improve ADL performance. Enhanced ADL ability may increase independence for children and adolescents and reduce the burden of care for parents/guardians.

Underpinning participation in many daily tasks are executive functions. This describes an umbrella term for functions such as planning, working memory, inhibition, mental flexibility, as well as the initiation and monitoring of action.[18] Children with mild CP have demonstrated impairments with executive function in multiple domains.[19] Therapies that not only target improvement in physical impairments but also

components of executive function have the potential to improve a child's performance and participation in more complex activities, including academic school performance.

An effective web based multi-modal training that enhances cognitive and motor abilities using multi-disciplinary virtual trainers may be a cost effective means of delivering therapy and facilitate translation of skills into home and community environments. This has significant implications for equity of access for children in diverse geographical locations. Move it to improve it (Mitii™) is an internet based multi-modal training program comprising upper-limb and cognitive training within the context of meaningful physical activity. Mitii™ detects bodily movements generated by a child using a green tracking band worn on the hand, head or knee. These movements are tracked by a web-camera attached to an internet connected computer. Mitii™ requires no specialist or costly equipment and can be delivered in the client's home. Physiotherapists, occupational therapists and psychologists act as virtual trainers remotely accessing the program to set up a series of 'games' via the program's 'cockpit'. These are graded regularly to deliver an incrementally challenging and individualized program.

The feasibility of delivering Mitii™ has been confirmed in a pilot study of 9 children achieving on average 35 minutes of training daily for 20 weeks (total dose 70 hours).[20] Compliance was high, with an average of 85% of children meeting or exceeding this dose. In a pre-post design, children made significant gains in motor and processing skills, functional strength, endurance, and a range of visual perceptual skills.

METHODS

Aims and Hypotheses

The main aim of this proposed study is to determine if 20 weeks of intensive Mitii™ training can improve upper-limb activity (unimanual and bimanual), occupational performance and cognitive skills in children and adolescents with CP compared to standard care. The secondary aim is to further our understanding of the central neurovascular mechanisms underlying changes in UL function, motor planning, and executive function (using functional magnetic resonance imaging (fMRI) and TMS to measure central activation in the parts of the brain controlling movement). This is an essential next step towards providing effective treatment and sustained outcomes. Further aims are to test the efficacy of Mitii™ across all dimensions of the ICF.

The primary hypothesis to be tested is:

1. In a waitlist randomized controlled trial, Mitii™ will be more effective than Usual Care (OT/PT) for children with congential hemiplegia (aged 8-18 years) to improve activity (unimanual capacity and bimanual performance) by a mean difference of 5 points on the Assisting Hand Assessment (AHA) and 10% decrease in time on the Jebsen-Taylor Test of Hand Function (JTTHF), and motor and process skills (AMPS) will improve by 0.5 logit scores following Mitii™ intervention.

Secondary hypotheses:

Mitii™ will be more effective than usual care at improving:

1. Use dependent neuroplasticity (cortical excitability on TMS) and neurovascular changes (fMRI), which will be more extensive and retained for longer;
2. Visual perception (visual discrimination, visual memory and visual sequential memory);
3. Executive functioning (EF; information processing, attentional control, cognitive flexibility, goal setting, working memory and behavioural manifestations of EF in everyday life) ;
4. Psychological functioning (SDQ);
5. Participation (LIFE-H) for categories of personal care, nutrition, education and recreation;
6. Occupational performance (COPM performance and satisfaction);
7. Functioning and participation domains of quality of life (CP-QOL-Child or CP-QOL-Teen);
8. Functional abilities in self-care and daily activities (MobQues28);
9. Physical activity capacity immediately following Mitii™ training (Functional strength: repeated sit to stand, half-kneel to stand and step up tests; and six-minute walk test);
10. Physical activity performance (ActiGraph®) and greater compliance with the national physical activity recommendations[21, 22];
11. Mitii™ will be more cost-effective compared with Usual Care as shown by resource use and effectiveness based on function (AMPS) and quality of life (CP-QOL).

Ethics

Full ethical approval has been obtained by the Medical Ethics Committee of The University of Queensland (2011000608) and the Royal Children's Hospital Brisbane (HREC/11/QRCH/35). Written and informed consent will be obtained from parents or guardian and all participants over 12 years of age by study coordinators and personnel upon entering the trial before matching and randomisation. The proposed Mitii™ clinical trial has been registered with the Australian and New Zealand Clinical Trials registration Trial: ACTRN12611001174976.

Study sample and recruitment

Children and youth with spastic type congenital hemiplegia aged 8-18 years will be recruited across Queensland and New South Wales, Australia. Potential study participants will be identified through a population-based research database, which currently comprises over 1600 children with CP at the Queensland Cerebral Palsy and Rehabilitation Research Centre (QCPRRC), the Queensland Cerebral Palsy Register (QCPR), Queensland CP Health Service and advertising to Occupational Therapists, Physiotherapists and Paediatricians at the Royal Children's Hospital, Brisbane and in the community. The recruitment process will target both publicly funded services and private practitioners with the expectation that the sample will be representative of children with congenital hemiplegia.

Inclusion and exclusion criteria

Children with mild to moderate congenital hemiplegia will be recruited, who are: (i) Gross Motor Function Classification (GMFCS) I or II[23]; Manual Abilities Classification scale (MACS) I, II, III[24]; (ii) aged 8-18 years with sufficient co-operation & cognitive understanding to perform the tasks; and (iii) able to access the internet at home (phone line or internet access). Children will be excluded if they have (i) received upper-limb or lower-limb surgery in the previous 6 months; (ii) unstable epilepsy (i.e. frequent seizures not controlled by medication), or (iii) a respiratory, cardiovascular or other medical condition that would prevent them participating safely in the Mitii™ training. Diagnosis of CP will be confirmed by a paediatrician or clinician and in accordance with published recommendations.[25]

Sample size

Sample size calculation is based on the primary hypothesis comparison between the functional effects of Mitii™ compared to standard care at 20 weeks on the AMPS. This study examines a continuous response variable from matched waitlist control and immediate-intervention participants with 1 waitlist control per immediate-intervention participant. In a previous study of Mitii™ the response within each group was normally distributed with standard deviation 0.58 on the AMPS.[20] To detect a clinically significant difference (0.35 units or greater) between groups with 80% power and alpha=0.05, 44 children are required in each group. Allowing for 10% attrition, the sample size will be 98 subjects. To assist in achieving this sample size, participants will be offered reimbursement of travel expenses and flexible appointment times and locations.

For hypothesis two, based on our previous randomised trial using 3T fMRI we see activation in the representative cortex for motor studies with good signal to noise ratio. Subject numbers will allow for some loss of information due to subject refusal (10%) and scans where motion is a confounder (10%). With 40 subjects in an analysis of baseline to week 20 changes on fMRI, this study will have 80% power to detect a difference between groups of 0.65 SD. If the supplementary motor area (SMA) is considered, given CV for control subjects performing motor tasks (CV of 11% in PM1 and 35% in SMA)[26], and activation signal of 1.5%, we are able to detect differences in % activation levels over time as small as 0.47.

Design

The efficacy of Mitii™ will be tested using a waitlist control assessor masked randomized trial RCT conducted according to CONSORT guidelines (see Figure 1). Participants will be consented to the study and then matched in pairs. All participants of the study will receive Mitii™ training. Within the pair, each participant will be randomized to either:

a) *Immediate intervention group*: Families return home with Mitii™ equipment and begin training immediately; Or b) *Waitlist delayed intervention (control) group*: Families continue care as usual for 20

weeks and then return to Brisbane for 1-day re-assessment then receive the same intervention as the immediate intervention group.

Children will not be provided with any concomitant treatments, such as arm splinting, casting or upper limb intramuscular Botulinum Toxin Type-A injections during the baseline to 20 week intervention period. Participants who have received intramuscular Botulinum Toxin Type-A in the upper limb the previous 2 months will have assessments and interventions postponed until after their standard follow up has been completed (usually 6-8 weeks post injection). All concurrent therapies provided by local services duration, frequency and content will be recorded by questionnaire at 20 week follow up.

(Insert Figure 1. CONSORT flowchart around here)

Randomisation

Children will be matched in pairs according to age (within 12 month age bands), gender and level of functional ability based on MACS level at screening. A matched pairs design is the design of choice as it minimises the likelihood of group differences at baseline that has often been present in rehabilitation studies.[27 , 28] Once matching has been achieved, children will be randomised within pairs (one member of each pair to be randomly allocated to each group) from concealed envelopes opened by non-study personnel. The randomisation process will involve randomly allocating a number "1" or "2' to each member of the pair. As each pair is entered, they will be allocated the next consecutive envelope, which will be opened by the non-study personnel who will read and record the treatment allocation from the paper inside the envelope. Treatment allocation will be recorded on a piece of folded paper inside each envelope in random order (either 1:Waitlist 2:Immediate; or 1:Immediate 2:Waitlist, with the sequence being computer generated). Study personnel will be informed of group allocation however participants and their parents/guardians will not be informed of their group allocation until after their baseline assessments.

Blinding

Functional MRI and TMS data will be qualitatively analysed by neurologists masked to group allocation. Paediatric neurologists with fMRI training will independently rate scan quality (0-5), region of activation, change over time and patterns of reorganization. Data on the AHA and MUUL will be rated from video recordings analysed by assessors masked to group allocation and assessment time point.

Adverse events

Any minor and major events associated with the training model will be screened at 20 weeks by open-ended questions.

Study Procedure

Children will attend the Queensland Cerebral Palsy and Rehabilitation Research Centre in Brisbane for 1 day for baseline assessments. Participants in the immediate intervention group will spend an additional day

for Mitii™ training and then return home with Mitii™ equipment and commence the training immediately. The delayed intervention (waitlist control) group will continue care as usual for 20 weeks and then return to Brisbane for 1-day re-assessment and then receive the Mitii™ training and equipment. For each participant, data will be collected at Baseline (T1). For the Immediate intervention group, follow up assessments will be conducted post intervention at 20 weeks post randomization (T2), and then retention (40-weeks post randomization, T3). For the Waitlist group, an additional baseline assessment will be conducted at 20 weeks post randomization (T2), and then post intervention at 20 weeks after commencing the Mitii™ training (40 weeks post randomization, T3). Retention of effects will be collected in the Waitlist group by an additional assessment at 60 weeks post randomisation (T4) (see Figure 1).

Mitii™ intervention

Mitii™ is delivered in the participant's home through an internet connected computer with a web-camera using a cloud server-based interactive training-system employing Adobe® Flash® technology. The system has been developed through collaboration between The Helene Elsass Centre, a private software development company (Head-fitted; Århus, Denmark) and the University of Copenhagen. It has now been made commercially available through collaboration between the Helene Elsass Centre and the Ministry of Research under the name Mitii™ (Move it to improve it; Mitii™ developments, Charlottenlund, Denmark).

A child is initially assessed by a multidisciplinary team (physiotherapist, occupational therapist, and psychologist) to ascertain fine and gross motor skills and cognitive abilities. A de-identified alias account is created for the child in Mitii™ and therapists develop an individually tailored group of tasks/games available in the program. The child then logs onto Mitii™ (through internet access) and completes the activities in his/her own home or local environment. Activities include gross motor control (e.g. unilateral and bilateral upper limb movement, sit-to-stand, balance) as well as cognitive tasks (e.g. matching, ordering, moving and tracking objects) (see Table 1). The combination of upper- and lower-limb gross motor, cognitive and visual perceptual training is designed to have a multi-modal effect by training multiple networks which then enhances performance in each area. It consists of a number of training modules or "games" in which the child has to analyse visual information, solve a cognitive problem (i.e. mathematical question or similar) and respond with a motor act (i.e. bend to pick up needle and pop the balloon with the right answer). The participant interacts with the system through movement of a green tracking band worn on the hands or head. The computer program identifies the movements of the child from video images sampled from a simple web-camera attached to the computer.

Mitii™ training

Participant logs into the Mitii™ website and access their individualized training programs at their convenience, enabling training to be completed at any time. The specific content and progression of the program will be decided from a weekly evaluation of participants' performance. The different modules will

be combined uniquely according to the specific cognitive and motor abilities of each child. The level of difficulty can be adjusted by increasing the difficulty of the perceptual (e.g. increasingly complex forms have to be correctly identified), cognitive (e.g. increasingly difficult mathematical questions) or motor challenges (e.g. child has to do more repetitions or work with higher load). This is completed by therapists (physiotherapist, occupational therapist and psychologists) who are in weekly email contact with the participants and their families. This has the effect that the participants and their parents have a private 'virtual' coach who oversees their training.

A series of individual tasks or games will be combined in a sequence to make a daily program of 30 minutes duration. Mitii™ should be completed for at least 30 minutes daily for six days per week for 20 weeks to provide sufficient training intensity (providing a total dose of 60 hours). Tasks can be divided into those training gross-motor or physical activity (eg. repetitive sit-to-stand exercises) or those combining cognitive or visual perception and an upper limb task (eg. moving the upper limb to solve a mathematic equation). To ensure each participant receives a similar training program, all sequences will comprise approximately 60% cognitive-upper limb and 40% gross-motor training tasks individualized to the child's abilities. Step blocks and balance foam can be added as the child progresses to add additional challenge to the tasks.

(Insert Table 1. Mitii Content around here)

Participant and data management

The percentage of eligible participants successfully recruited, and numbers of eligible participants who choose not to participate will be recorded. Participant retention will be recorded throughout the trial period. All data will be analysed by intention to treat, whereby a participant's assessment from the last available time-point is carried forward in the event of study withdrawal or loss to follow-up. Treatment dose is automatically recorded by the Mitii™ program and will be monitored by the therapists. Strategies to manage engagement in the program will be discussed with the participant and parent/guardian during their initial Mitii™ training. All participants will receive a Mitii™ rewards chart which segments the 20 week program into four 5 week blocks and allows small rewards to be decided in advance for completing each stage. Other strategies such as parent/guardian involvement, feedback, positive reinforcement and incorporating Mitii™ into the family routine will also be discussed. Therapists will contact participants via email, telephone and Skype to troubleshoot any technical programs and to support engagement.

Classification measures

a) Classification of the brain lesion

Brain lesion will be classified using a qualitative and quantitative structural MRI classification system. The classification system is based on the presumed timing and nature of the insult that resulted in CP including both genetic and non-genetic aetiologies such as cortical malformations & hypoxic ischaemic injury[29] and a quantitative system to grade the location, extent and severity of the brain lesions with an asymmetry index.[30]

b) Gross Motor Function Classification System (GMFCS)

The GMFCS classifies the child's ability to carry out self-initiated movements related to sitting and walking across 5 levels.[23] The GMFCS has strong construct validity with the Gross Motor Function Measure (r=0.91)[31] and good inter observer reliability between professionals and between professionals and parents.[32] In this sample of children with hemiplegia, all children will be GMFCS level I (walks without limitations) and II (walks with limitations).

c) Manual Abilities Classification System (MACS)

The MACS classifies the child's ability to handle objects in daily activities on one of 5 levels.[24] The MACs has reported construct validity, and excellent inter-rater reliability (Intraclass Correlation Coefficient [ICC]=0.97 between therapists and ICC=0.96 between therapists and parents).[33] All children in the sample will be MACS level I (able to handle objects easily and successfully), level II (able to handle most objects but with somewhat reduced quality and/or speed of achievement so that alternate ways of performance might be used) or level III (handles objects with difficulty; needs help to prepare and/or modify activities).

d) Anthropometric data

Height will be measured to the nearest 0.5 centimetre while the child is standing with his or her back against a wall.

e) Wechsler Intelligence Scale for Children–Fourth Edition Short Form (WISC-IV SF)

The seven subtest, short-form version of the Wechsler Intelligence Scale for Children fourth edition (WISC-IV) will be used to measure intellectual functioning across four indices: verbal comprehension (VCI), perceptual reasoning (PRI), working memory (WMI), and processing speed (PSI). An overall short form, full scale intellectual functioning (FSIQ) score will be calculated from the index scores. The VCI consists of the Vocabulary and Similarities subtests, the PRI is comprised from Block Design and Matrix Reasoning subtests, the WMI is derived from the Digit Span subtest and the PSI from the Coding and Symbol Search subtests. In the Vocabulary subtest, children will name pictures or provide definitions of words (e.g., "what is a hat"). For Similarities, children will describe how two words that are common objects or represent common concepts are similar (e.g. "in what ways are a cat and mouse alike"). In Block Design,

children will reproduce a set of red-and-white blocks either modelled or printed two-dimension geometric patterns within a specified time limit. Matrix Reasoning will involve the child being shown an array of pictures with one missing square and they will need to select the picture that fits the array from five options. In Digit Span, children will repeat a string of verbally presented numbers in both a forward and backward direction. Finally, in Symbol Search, children will visually scan a search group of symbols and indicate whether or not a target symbol is in the search group and in Coding, children will transcribe a digit code. Both of the Symbol Search and Coding tasks need to be rapidly completed within two minutes. Index scores will be converted into scaled scores in accordance with normative data based on the child's age and gender (mean=100, standard deviation[SD]=15).[34, 35] All index scores of the WISV-IV SF have shown moderate to high levels of internal consistency (α=0.87–0.96) and are equivalent to those documented for the full WISV-IV, with the exception of the WMI which is marginally lower than its full length equivalent.

Neurovascular measures

Neurovascular outcomes will be collected at baseline and 20 weeks.

(a) Whole-brain functional MRI studies:

Functional imaging at 3T on a Siemens MAGNETOM Trio MR scanner will be conducted on the research dedicated scanner at the Centre for Advanced Imaging at the University of Queensland. The 3T scanner provides approximately twice the signal to noise ratio compared to conventional 1.5T scanners which will reduce the time in the scanner and improve the resolution of data collected. Published methods[4] will be utilized for conducting serial fMRI studies preparing in a mock MRI scanner and the motor paradigm will consist of a 2-condition block design (wrist extension compared to rest), visually cued via instructions projected on a screen, timed with an auditory cue for the rate of movement at 2Hz. The task and rest periods are 30 seconds with the activation cycle repeated 4 times.

Children with sufficient comprehension will also complete a complex motor task as an additional task in the scanner. This task is a timing versus sequencing task performed in a block design (two runs of six minutes each), where the subject alternates between a block of single index-finger button-pressing and a block of random sequences of 3-finger button-presses. For the sequence task, visual cues of "123, 321, 213" numbers denote a random sequencing of pushing three buttons with their index, third and fourth fingers on buttons with their dominant hand. This complex task is designed to differentiate activation in the primary motor cortex and different aspects of the basal ganglia circuit. The rationale behind the simple and complex movement is based on previous studies that showed these movements are able to induce activation of the motor cortex and basal ganglia circuits.[36] Notably increased complexity of finger movements increases activation of the basal ganglia circuit, and thus provides an ideal model to utilise fMRI to locate function specific regions of the cortex associated with finger movements.

An additional 5 minutes of resting-state fMRI will also be collected for analysis of functional connectivity (FC). Tasks performed prior to resting-state fMRI can influence functional connectivity.[37] The movements performed in the scanner will be rated for speed, range of motion, ability to isolate and the presence of mirror movements in the contralateral hand. Functional MRI will be acquired using a BOLD acquisition sequence (gradient-recalled-echo (GRE) echo-planar imaging (EPI), repetition time (RT)=3.0s, Echo Time (TE)=30ms, Flip angle=850, Slice thickness=3mm, FOV=216mm, 44 slices, 72 x 72 matrix yielding an in-plane resolution of 3.0mm x 3.0mm). A single set of T2-weighted anatomical, FLAIR and 3D T1 volumes will also be collected. Functional MRI image processing, analysis and visualisation will be performed using iBrain™ software[38] and SPM software (Welcome Dept of Imaging Neuroscience, London, UK). Detailed information about pre-processing and post processing of the fMRI has been published.[4] The same processing and established analysis of data will be utilised for this proposed Mitii™ project. In addition, temporal autocorrelation will be modelled using a white noise and autoregressive AR(1) model within SPM. Motion correction parameters will be included as covariates.[39] Due to heterogeneity in lesion location and size across participants, group analysis of intra-participant change in activation will be using region of interest with iBrain™ software.[38]

b) Diffusion imaging and structural connectivity

Diffusion-weighted images will be acquired using a twice-refocussed single-shot EPI sequence (64 directions, b-value 3000 s/mm2, 60 contiguous slices with 2.5 mm thickness covering the whole brain, in-plane resolution 2.35 x 2.35 mm, acquisition time approximately 10 minutes). White matter tractography will be performed with MRtrix using probabilistic tractography, with fibre orientations obtained using constrained spherical deconvolution, taking into account the presence of crossing fibres.[40,41] An automated technique has been developed to generate whole brain tractograms, from which individual white matter pathways (e.g. motor and sensory) can be extracted for statistical analysis.[42]

To improve our understanding of cortical plasticity post training, cortical reorganisation will be investigated using a combined fMRI-structural connectivity analysis strategy. In this approach, regions of corticomomtor activation derived from the fMRI analysis (generated post therapy) will be used as target masks for extracting white matter motor pathways. This will enable the identification of all corticomotor networks exhibiting plasticity as a result of the motor training paradigms. Plasticity within these neural circuits will be measured by comparing apparent fibre density (AFD)[43], a quantitative measure of the organisation of WM fibres, derived over the entire pathway. This strategy enables both an anatomical view of cortical reorganisation and quantitative measures of altered connectivity induced by therapy. We also propose to measure plasticity based on an analysis of structural connectivity. In this approach, connectivity matrices will be generated based on parcellation of cortical and subcortical using Freesurfer image analysis suite (http://surfer.nmr.mgh.harvard.edu) and the whole brain tractograms, as outlined above. Hit-testing every streamline with every cortical parcellation will generate the connectivity matrices. Diffusivity indices

(Fractional Anisotropy [FA] and Mean Diffusivity [MD]), quantitative markers of the integrity of white matter, will be encoded within the connectome to enable assessment of motor task generated reorganisation.[44, 45] Network based statistics (NBS)[46] will be performed between the FA and MD connectomes for the control (CP without intervention) and intervention groups to identify statistically significant cortical networks that are associated with neural reorganization.

c) Transmagnetic stimulation (TMS)

TMS (MAGSTIM 200) will be performed on all participants in both groups at baseline then at 20-22 weeks post intervention. The baseline study will be conducted following fMRI to prevent contamination of fMRI findings by TMS. A figure of 8 TMS coil is used to stimulate the brain and surface EMG electrodes are used to record motor evoked potentials (MEPs) from the target muscles, right and left abductor pollicis brevis (APB). TMS will be performed at the same time of day to reduce variability. MEPs will be recorded on a Synergy EMG machine using band-pass filtering 10Hz–5kHz, sweep speed 100ms and gain 100 V/div. Auditory EMG feedback will be given to ensure voluntary relaxation of the target muscles during stimulation.

The experimental session will record the following parameters:

i) Motor Threshold (MT): Stimulation will commence at 30% of maximum output and increase in 5% increments until the motor evoked potential (MEP) is established. 1% changes in intensity will then be used to calculate the threshold value. Motor threshold is defined as the lowest level of stimulus intensity which produced a MEP in the target muscle of peak-to-peak amplitude > 100 μV on 50% or more of 10 trials.[47]

(ii) MEP Recruitment Curves: The maximum compound muscle action potential (CMAP) amplitude of the resting APB will be determined by supramaximal stimulation of the median nerve at the wrist. For each participant, the average of the CMAP amplitudes obtained after three stimuli will be calculated as was defined as 100%.[48] MEPs obtained by Single pulse TMS using different randomized stimulus intensities of 110, 120, 130, and 140% MT will be expressed as a percentage of the CMAP in order to obtain recruitment curves.[49] An average of 10 peak-to-peak MEPs recorded for each stimulus intensity will be calculated.

For motor thresholds and recruitment curve measurements, the stimulus will be delivered to the contralateral cerebral hemisphere using the appropriate direction of coil current flow (anticlockwise for left cortical stimulation and clockwise for right cortical stimulation). This will be performed using a flat circular 9 cm diameter magnetic coil (14 cm external diameter) connected to a Magstim stimulator (Magstim, Whitland, Dyfed, United Kingdom). The centre of the coil will be positioned over the vertex and held in a plane tangential to it. The coil will be held in place by a support stand, and its position will be checked regularly through each experiment.

(iii) Ipsilateral Motor Pathways: This will be performed using a figure-of-eight–shaped coil (outer diameter of each loop 70 mm) connected to a Magstim stimulator (Magstim, Whitland, Dyfed, United Kingdom). The

coil will be placed tangentially over the ipsilateral hand motor cortex with the handle pointing back and laterally 45° away from the midline at the optimal site for the activation of the APB. This is thought to be the best position for activating the pyramidal cells trans-synaptically and preferentially elicits late I-waves.[50] The direction of current induced in the brain will be anterior to posterior.

Primary outcome measures

a) Assessment of Motor and Process Skills (AMPS)

The AMPS is a standardized, criterion-referenced, observational assessment of the motor abilities of people two years of age and older. An OT evaluates the quality of a person's ADL task performance at the level of activity and participation in a culturally relevant manner.[51] For the assessment, the patient selects a minimum of two daily activities (e.g. dressing, eating, food preparation) from 116 task options, for which the quality of activity is scored on the degree of exertion, efficacy, confidence and independence in 16 ADL motor and 20 ADL processing skills. The child is also given ratings for overall functioning levels. The performance of children in each of the motor and processing skills is scored from 1-4 (1=deficient performance that impeded the action progression and yielded unacceptable outcomes, through to 4=competent performance that supported the action progression and yielded good outcomes). These raw scores are entered into the AMPS computer-scoring software, and converted through many-faceted Rasch (MFR) analyses into linear ADL motor and ADL process ability measures, ranging from 4 to -3 for motor skills and 3 to -4 for processing skills. Test-retest reliability of the AMPS is high for both motor (r=0.9) and process (r=0.87) skill scales in an adult population.[51] This measure is also very sensitive to change, as it evaluates the smallest possible units of ADL task performance and involves 116 task options which vary in challenge.

b) Assisting Hand Assessment (AHA)

Bimanual performance will be assessed using the AHA. This is a Rasch analysed measure of the effectiveness with which a child with a unilateral impairment makes use of his/her impaired hand in bimanual tasks.[52] The test consists of twenty-two items that are videotaped and each scored on a four point rating scale, yielding a range of scores between 22 and 88. Scaled scores are calculated by transforming the total raw score to a percentage and range from 25 to 100. Rasch analysis allows conversion of these ordinal scores into logits (log odds probability units) which are equal interval measures. Inter-rater and intra-rater reliability is high for summed scores (ICC=0.98 and 0.99 respectively). There are three versions of the AHA; small kids (18 months to 5 years), school kids (6 to 12 years) and an adolescent version in development (>13yrs). Test-retest reliability is high for small kids (ICC=0.99) and school kids (ICC=0.98) and reliability between the two forms (small kids versus school kids) is also high (ICC=0.99).[53] The AHA is responsive to change due to an UL intervention.[54] Investigation of reliability yielded a smallest detectible

difference of 3.89 raw scores for the small kids and 3.65 raw scores for the school kids version.[53] The AHA requires standardised training and certification of raters.[52] The AHA will be scored by certified raters who will be masked to group allocation and order of assessment.

c) Jebsen Taylor Test of Hand Function (JTTHF)

Activity limitations will be measured for unimanual capacity using the JTTHF.[55] The JTTHF evaluates speed and dexterity in 6 timed tasks with an individual score for each upper limb. The tasks are of varying complexity and use everyday items to assess grasp and release abilities. The original test designed and validated in adults and typically developing children will be modified with omission of the writing activity and by reducing the maximum allowable time of each task to 2 minutes to both reduce frustration and allow comparison with similar studies in children with congenital hemiplegia.[27,28,56] The JTTHF has been shown to be responsive to change due to an intervention; however there are some difficulties with stability of test-retest performance in the unimpaired limb.[27,28,56,57] There is high inter-rater reliability (ICC=0.82-1.0) for each subtest and test-test reliability with 5 patients and 2 raters (r=0.84-0.85) in an aging adult population.[58] The JTHFT has demonstrated good responsiveness to detect change due to interventions that improve upper limb speed and manipulation.[27]

Secondary outcomes will assess Mitii™ against all dimensions of the ICF:

Body Structure and Function domain

a) Executive Functioning

Executive functioning will be assessed across four domains: attentional control, information processing, cognitive flexibility, and attentional control in accordance with Anderson's paediatric model of executive functioning.[59] A neuropsychological test battery will be utilised to assess these domains comprising of subtests from the Delis-Kaplan Executive Function System (D-KEFS)[60] and the Wechsler Intelligence Scale for Children Fourth Edition (WISC-IV).[35] Behavioural manifestations of executive functioning in everyday life will also be assessed using the Behaviour Rating Inventory of Executive Function (BRIEF).[61] All scores will be converted into scaled scores according to normative data based on the child's age and gender.

i) Colour-Word Interference Test (from the D-KEFS)

The Inhibition condition from the Colour-Word Interference Test will be used to measure attentional control. Children will be required to name the ink colour that colour words are printed in across five rows (e.g., say "red" for the word "blue" printed in red ink). The total time (seconds) taken to complete the task will be the primary outcome measure, with longer time indicative of poorer attentional control. Raw scores will be converted into scaled scores (mean=10, SD=3). Excellent test-retest reliability has been shown for the Colour-Word Interference Test (r= 0.90).[62]

ii) Trail Making Test (from the D-KEFS)

The Number Sequencing condition from the Trail Making Test will be used to measure attentional control and the Number-Letter Switching condition will be used to measure cognitive flexibility. In Number Sequencing, children will connect numbers printed on an A3 sheet in numerical order from 1 – 16, while in Number-Letter Switching, children will be required to switch back and forth between connecting numbers in numerical order and letters in alphabetical order, also printed on an A3 sheet, from 1 – 16 and A – P (e.g., "1-a-2-b-3-c"). The total time (seconds) taken to complete each task will be recorded, with a longer time indicating greater difficulty with attention control or cognitive flexibility. Raw scores will be converted into scaled scores (mean=10, SD=3). Adequate test-retest reliability for Number Sequencing (r= 0.77) and Number-Letter Switching (r=0.20-0.55) has been documented.[62]

iii) Tower Test (from the D-KEFS)

The Tower Test will be used to measure goal setting. Children will move five disks across three pegs to build a target tower as illustrated in a picture within a specified time limit. They will be instructed to use the least number of moves possible to complete the tower, that they can only move one disk at a time and that they must never place a larger disk on top of a smaller disk. The total achievement score, which is based on the total number of moves needed to build the tower, and the total number of rule violations will be used to measure goal setting abilities. The lower the achievement score and the higher the rule violations score indicate greater goal setting difficulties. Raw scores will be converted into scaled scores (mean=10, SD= 3). The Tower Test has a moderate to high level of internal consistency (α=0.43-0.84) and adequate test-retest reliability (r= 0.51).[62]

iv) Digit Span (from the WISC-IV)

Digit Span Backwards is a verbal working memory task that requires children to temporarily store and manipulate information and will be used as a measure of cognitive flexibility. A string of numbers will be given verbally to the children increasing from two digits to eight, and they have to repeat the number string in the reverse order (e.g. if "3-7-2" the child should say "2-7-3"). A score of one is given to each string correctly repeated in reverse order with a lower overall score indicating poorer cognitive flexibility. Raw scores will be converted into scaled scores (mean=10, SD=3). Digit Span Backwards has been shown to have a good internal consistency (α=0.80) and adequate test-retest reliability (r=0.74).[63]

v) Coding (from the WISC-IV)

Coding will be used as a measure of information processing. Children will have to copy simple geometric shapes that are paired with numbers within two minutes. The overall number of correctly copied geometric shapes will be calculated, with a lower number indicating poorer information processing. Raw scores will be converted into scaled scores (mean=10, SD=3). Good internal consistency (α=0.82) and test-retest reliability (r=0.81) for Coding has been shown.[63]

vi) Symbol Search (from the WISC-IV)

Information processing will also be assessed using Symbol Search. Children will visually scan for a target symbols in groups of five symbols and indicate whether the target symbol is in the group by placing a line through the word 'yes' or 'no'. Children will be told to work as fast as they can in two minutes. The total number of correctly identified symbols minus the total number of incorrectly identified symbols will be calculated, with lower scores indicating poorer information processing. Raw scores will be converted into scaled scores (mean=10, SD=3). Symbol search has been documented to have an adequate internal consistency (α=0.79) and a high level of test-retest reliability (r=0.80).[63]

vii) Brief Rating Inventory of Executive Function (BRIEF)

In addition to cognitive measures of executive functioning, behavioural manifestations of executive functions in everyday life will be measured using the BRIEF, an 85 item parent-rated questionnaire. Parents rate items (e.g. "does not think before doing") on a three-point scale ranging from 1 (*never*) to 3 (*often*). Two index scores will be obtained from the BRIEF: (1) the behavioural regulation index (BRI), which is derived from four subscales: initiate, working memory, plan, organisation of materials and monitor, and; (2) the metacognition index (MCI), which is derived from three subscales: inhibit, shift, and emotional control. The BRI and MCI will then be combined to form an overall global executive composite score (GEC). Raw scores will be converted into *T* scores (mean=50, SD=10), with higher *T* scores indicating a greater level of executive dysfunction. A *T* score of 65 and above, which is 1.5 standard deviations above the mean, will be used as the cut-off for abnormal elevations across all scales.[61] The BRIEF has been found to be ecologically valid measure of executive functioning and has been shown to have good internal consistency (α=0.80 – 0.98) and high test-retest reliability on the BRI (r= 0.92), MCI (r=0.88), and the GEC (r=0.86).[61]

b) Test of Visual Perceptual Skills (TVPS)

The TVPS-3 is comprised of seven subscales: visual discrimination, visual memory, visual spatial relationships, form constancy, visual sequential memory, figure-ground, and visual closure.[64] Performance will be determined by the number of correct answers in each test (maximally 16 in each of 7 tests). Performance will be scaled according to normative data and converted into a percentage score for the age group. The TVPS-3 is a reliable and valid measure of visual perception in persons aged 4 to 18 years.[64]

c) The Melbourne Assessment of Unilateral Upper Limb Function (MUUL)

The MUUL measures both upper limb impairment and quality of upper limb function.[65] It is designed for children aged 5 to 15 years with CP and consists of sixteen criterion-referenced items measuring aspects of reach, grasp, release, and manipulation. The maximum possible raw score is 122, with raw scores being computed into percentage scores. Inter-rater and intra-rater reliability for the MUUL is very high for total test scores (ICC=0.95 and 0.97, respectively) and moderate to high for individual items (ICC=0.69 – 0.91).[66] The MUUL also has good internal consistency (α=0.96).[66] Construct and content validity for the MUUL was established during test development.[66]

d) Lower Limb Functional Strength

Mitii™ will focus on training functional strength therefore assessment of Repetition Maximum (RM) during functional exercise will be used to assess strength. Functional strength will be tested according to the protocol outline by Verschuren et al.[67]

i) Lateral step-up

This is the number of step up repetitions onto a bench during 30 seconds. This is tested with the stool height adjusted to the GMFCS level (I,II=15-20 cm stool). The child stands with the leg being tested on the stool and the non-testing leg on the floor, with feet parallel and shoulder width apart. The child then extends the test leg (on the stool) to within 10˚ of full knee extension, so that the non-test leg is off the ground, then lowers the foot back down to the floor until either the toes or heel touches.[68] This is considered one full cycle. The child should maintain dorsiflexion of the non-test foot and a horizontal pelvis throughout by keeping hands on hips throughout the test. This is repeated and the number completed within 30 seconds is recorded commencing with the right leg for all children. This is then repeated for the left leg.

ii) Sit-to-stand

This tests the number of sit-to-stand repetitions that can be achieved within 30 seconds, with sit-stand-sit considered a full cycle. The seated position is reached when the knees and hips are in 90˚flexion. Full standing is considered within 15˚ full extensions of the hips and legs. The sit-to-stand must be achieved with arms free and without any support from the chair or the child's body.

iii) Half kneel to stand

This is the number of repetitions of half kneel to stand that can be completed in 30 seconds. The child is positioned in half-kneeling on a mat, with the buttocks clear of the lower leg and/or the floor. The child must then assume a standing position without using the arms or any external support, such as the floor or furniture. Repetitions are counted each time the participant achieves a standing position where both legs and hips are within 15˚ of full extension. This is recorded commencing with the right leg in front, and then repeated with the left leg in front.

For all tests, children will be given 2 practice repetitions per extremity prior to formal testing. Between each practice and testing, 30 seconds rest will be provided. Between tests 180 seconds (3 minutes) rest will be provided. The tests will be assessed in the above order: Lateral step test right, lateral step test left, sit to stand, half kneel to stand right, half kneel to stand left. Children will be instructed to perform as many repetitions as possible in 30 seconds and will be verbally encouraged.

Acceptable inter-tester reliability has been demonstrated for functional strength testing in 25 children with CP ((ICC>0.91; Coefficient of variation (CV)=12.1-22.7%) . Reliability for the tests were strong (Lateral step up ICC=0.94; Sit to stand ICC=0.91; Half kneel to stand ICC=0.93 to 0.96). Mean repetitions for the lateral step up were 13.2 (SD=10.5; standard error of measurement (SEM)=2.4 reps; CV=17.8%) for

the left side, and 12.6 (SD=10.4; SEM=2.6 reps; CV=22.7%) for the right side. Mean number of repetitions for the sit to stand was 14.4 (SD=5.0; SEM=2.6 reps; CV=22.7%). Half kneel to stand was less, with an average of 7.5 reps (SD=5.5; SEM=1.1 reps; CV=28.6%) for the left side and 6.0 (SD=5.3; SEM=1.4 reps; CV=39.9%) for the right side.[67]

e) Six Minute Walk Test (6MWT)

The 6MWT is a simple, sub-maximal clinical exercise test which measures the distance walked (6MWD) under controlled conditions over six minutes. The 6MWT has been found to be reliable in independently ambulant adolescents with CP.[69] In this population, test-retest reliability was excellent (ICC=0.98). Percentile curves for the 6MWT have been created, though these were from 1,445 typically developing Chinese children aged 7-16 years.[70] No reference curves for children and adolescents with CP exist. While children with CP may exhibit lower 6MWD compared to typically developing children due to muscle spasticity, aberrant gait patterns and functional restrictions, GMFCS Levels I and II are able to walk with little to no restrictions therefore one could expect similar test results to a typically developing child. The 6MWT will be performed using standardized verbal encouragement asking the children to walk as fast as possible along a flat, straight, 10m corridor with cones marking the turn-around at each end as per Maher et al.[69]

f) Passive Range of Motion

Upper and lower limb passive range of motion for the unimpaired and impaired side will be assessed by occupational and physiotherapists at baseline.

Activity domain

a) Habitual Physical Activity (HPA)

HPA will be measured using ActiGraph® GT3X+ tri-axial accelerometer (Pensacola, FL). This detects accelerations of a magnitude and frequency with raw acceleration data, proportional to the amount of HPA done by an individual. ActiGraph® units will be fitted during assessment and worn during waking hours for 4 days. After 4 days it will be returned by registered post for data extraction and analysis. An activity diary will be coupled with an ActiGraph® to detect and log accelerations of human movement. Data will be considered for analysis where accelerations are recorded for >4 hrs per day. Analysis will convert counts to activity intensity using Evenson cut points[71] to allow comparison to the national physical activity guidelines.[21,22] The ActiGraph® will also be set up to detect step counts.

The ActiGraph® is a valid instrument to detect HPA in children and adolescents with CP. The ActiGraph® accelerometer is strongly correlated to direct observation during structured activity and free play, and more accurate than heart rate.[72] It has also demonstrated excellent classification accuracy, and

Evenson cut points were found to be the most accurate for adolescents with CP.[73] In typically developing children, the reliability of accelerometers has been shown to increase with increased recording days (ICC: 0.45 for 1 days to 0.9 for 8 days).[74] Seasonal variation has been demonstrated with less activity being performed in the winter months (ICC=0.54).[74] Age has also been found to influence reliability, with typically developing primary school aged children participating in more moderate to vigorous physical activity on weekends and exhibiting less day-to-day variability in activity, requiring only 4-5 days monitoring, in contrast to adolescents who exercise less on weekends and require 8 or 9 days of monitoring.[75] Acceptable reliability has been found with 4 days of monitoring (r=0.75-0.78).[76] However, there is no evidence that documents the reliability of the ActiGraph® in children with CP. Children in the present study will be fitted with an ActiGraph® accelerometer to collect 4 days of free living activity after the assessments and training days. Additionally, further work on the reliability of the ActiGraph® in children and adolescents with CP will be conducted. Participants will rest for a 5 minute period and then conduct selected light, moderate and vigorous assessment tasks, interspersed with 5 minute rest periods in a standardized manner whilst wearing an ActiGraph® monitor and concurrently measuring heart rate and classifying the activity using direct observation. All participants will have the option to undergo this assessment during the assessment and Mitii™ training 2 day visit.

b) Mobility Questionnaire (MobQues)

The MobQues measures mobility of children with CP by assessing amount of difficulty the children have in executing mobility activities. It addresses mobility limitations a child experiences in everyday life and covers a range of severity levels. The MobQues focuses on 47 mobility activities, from which the MobQues47 and the MobQues28 scores can be calculated by scoring 47 or 28 mobility activities, respectively. Response options of the MobQues are: Impossible without help (score 0), very difficult (score 1), somewhat difficult (score 2), slightly difficult (score 3), not difficult at all (score 4).Total scores are calculated by adding all item scores (range 0–4) divided by the maximum possible score and multiplied by 100 to obtain scores on a scale of 0 to 100 (with a low score representing severe limitations in mobility):MobQues47=(Σ item / 188)·100; MobQues28=(Σ item / 112)·100. For research purposes, the shorter version (MobQues28) is recommended due to better measurement properties, whereas the MobQues47 can be used for clinical applications. Content validity of the instrument has been demonstrated as 46 of the 47 test questions relate to the 'mobility' according to the definitions of the ICF. Construct validity was demonstrated as MobQues scores decreased with increasing GMFCS level ($p<0.001$). In a subgroup of 162 children, MobQues score was positively correlated to GMFM-66 (MobQues47, r=0.75; MobQues28, r=0.67, $p<0.001$).[77] It has also been demonstrated to be a reliable instrument.[78] For the strong inter-rater reliability was found for theMobQues47 (ICC=0.92) and MobQues28 (ICC=0.87). The SEM was 7.8 and 8.9 respectively. As expected, the intra-rater reliability was higher for both MobQues versions (ICC=0.96–0.99; SEM=3.5–4.9).[78] The English version has not yet been cross-validated therefore the results

demonstrated may differ slightly to that in an English speaking population. Data sharing has been arranged with the MobQues authors to enable cross cultural validation of this tool. To allow this the MobQues47 clinical version will be used at baseline to obtain a full dataset, and then the MobQues28 will be collected at subsequent assessments. The MobQues28 will be extracted from the baseline assessment to allow comparison across time points.

Participation domain

a) Canadian Occupational Performance Measure (COPM)

Individualised goals will be measured using the COPM to evaluate self-perception of occupational performance over time.[79, 80] The COPM will be administered by one OT with the child/adolescent and parent. The COPM is a standardised individualised, client centred measure that evaluates client's self-perception of occupational performance. Clients identify areas of difficulty in everyday occupational performance and rate their performance and satisfaction for each problem on a scale from 1 to 10. An average score for performance and satisfaction is calculated.[67] The COPM was designed for all ages and disability groups. There is good evidence of construct, content and criterion validity. The retest reliability of the performance and satisfaction scores on the COPM is high (ICC=0.76-0.89).[80-82] The COPM has demonstrated responsiveness to change in paediatric clinical trials,[83, 84] and a 2 point change on COPM performance has been reported as being clinically significant.[79]

b) Assessment of Life Habits (LIFE-H)

The LIFE-H is designed for children aged 5 to 13 years and measures life habits in home, school and neighbourhood environments.[85, 86] It is a questionnaire completed by the parent/caregiver about the child. The child form is based on an adult version. The long form consists of 197 items divided into 12 categories and includes regular activities (e.g. eating meals, communication, and mobility) and social roles. A weighted score ranging from 0 to 10 is generated for each category and overall total.

Evidence of construct validity and criterion validity, with strong correlations between the LIFE-H and PEDI and Functional Independence Measure for Children (WeeFIM), are established.[85, 87] Adequate to excellent internal consistency (α=0.73–0.90 for categories, 0.97 for daily activities and 0.90 for social roles), intra-rater (ICC=0.83–0.95 for daily activities), inter-rater (ICC=0.8–0.91 for daily activities and ICC=0.63–0.9 for social roles) and test-retest reliability (ICC=0.73 for total score) have also been established.[88] Four categories will be evaluated in this study including nutrition (e.g. mealtime activities), personal care (e.g. dressing), education and recreation. These areas were considered to reflect many of the identified difficulties confronted by children with congenital hemiplegia that might be amenable to the intervention program.

c) Participation and Environment Measure for Children and Youth (PEM-CY)

The PEM-CY is a newly developed, parent-report measure for children aged 5 to 17 years that examines participation and environment across three settings: home, school, and community.[89] No interview is required for administration with parents completing the assessment either online or using a paper based form, which supports its use in this large-scale study. The PEM-CY examines the extent to which young people participate in important activity areas within the home, school and community environments, and the extent to which particular features of these environments are perceived to support or challenge the young person's participation. Evidence of the psychometric properties of this new instrument are limited to date, however data from a sample of 576 young people showed internal consistency was moderate to good (□>0.59) across the scales. Test-retest reliability was moderate to good (ICC>0.58) across a 1-4 week period using the online version of the assessment.[90] The PEM-CY will be collected at baseline.

d) Strengths and Difficulties Questionnaire (SDQ)

The SDQ will be used to measure parents' perceptions of prosocial and difficult behaviours in their child.[91, 92] The SDQ has a total of 33 items. The first 25 items are divided into 5 scales and assess the frequency of emotional symptoms, conduct problems, inattention/hyperactivity, peer problems and prosocial behaviour (e.g. "considerate of other people's feelings"). These items are rated upon reflection of the last six months on a three-point scale, from zero (*not true*) to two (*certainly true*). A total score for each scale (0-10) and an overall total difficulties score (0-40) will be calculated, with higher scores indicating more distress on all scales except prosocial behaviour. A clinical cut-off of ≥17 will be utilised on the total difficulties score. The total score on the 5 scales and the overall total difficulties score will be utilised as measures of the child's psychological functioning. Moderate to high internal consistency (α=0.73-0.82) and test-retest reliability (*r* =0.77–0.85) has been shown on the overall total difficulties score.[93, 94]

Cerebral Palsy Quality of Life (CPQOL)

QOL will be measured using a condition specific measure, either the CPQOL-Child parent report[95], or for children 9 years or age or older, the CPQOL-Teen.[96] Results of factor analysis demonstrated that the CPQOL measures 7 broad domains of quality of life: social wellbeing and acceptance, functioning, participation, physical health, emotional wellbeing, access to services, pain, impact of disability and family health. The psychometric properties of the CPQOL-Child are excellent, with strong internal consistency (□=0.74-0.92 for parent-proxy report; □=0.80-0.90 for child self-report). Test re-test is adequate (ICC=0.76-0.89) and it is moderately correlated with generic QOL and health (r=0.30-0.51).[97, 98] The CPQOL-Teen, for adolescents aged 13-18 years has strong psychometric properties, with strong internal consistency (□=0.81-0.95 for the primary caregiver report; □=0.84-0.96 for the adolescent self-report) and strong test re-test reliability for adolescents (ICC=0.84-0.87) and for primary caregivers (ICC=0.72-0.92). In terms of validity, all domains of the CPQOL-Teen parent report (r=0.40-46) and adolescent report (r=0.58-

0.68) were correlated with a generic QOL instrument.[99]

Environmental and Personal Factors

A study questionnaire was developed to capture demographic information that has been shown in the literature to influence a child's participation. These include family ethnicity, household income, parental education and employment, family structure and supports, and family interests. This will be collected at baseline assessments then any changes measured at subsequent assessments. A measure of social advantage/disadvantage will be derived from postcode of residence using the Index of Relative Socio-economic Advantage/Disadvantage from the Australian Bureau of Statistics.[100] Deciles will be reported on a continuum with lower scores reflecting greater socio-economic disadvantage and higher scores reflecting socio-economic advantage.

Economic Analysis

An economic analysis will be conducted to synthesise health outcomes and costs to both families and health systems. Costs will be obtained for healthcare use (measured through self/proxy reports) and measured directly for the intervention (including the number and duration of visits by the intervention team). Standard costs will be assigned to the resource use (e.g. medical care, allied health visits and diagnostic/investigational services will be assigned a cost according to a fee schedule and medications will be costed based on their description, dosage regimens, and whether or not they are listed on the Pharmaceutical Benefits Schedule). Outcomes will be measured as change in Quality of life from baseline to end of intervention based on the CP-QoL. The base case model timeframe will be 20 weeks consistent with the trial follow up and all costs and outcomes will be extrapolated for at least 10 years, with an annual discount rate of 5% applied to both costs and outcomes, to estimate future expected costs and benefits. Sensitivity analyses will be undertaken around key parameters to assess the effect on results from varying these parameters. These can then be compared with other healthcare interventions and value for money judgments made by policy makers. An incremental cost-effectiveness ratio (i.e. $[cost_{MiiTii} - cost_{usual\ care}]/[outcome_{MiiTii} - outcome_{usual\ care}]$ will be calculated.

Statistical analysis

Analysis will follow standard principles for RCTs, using two-group comparisons on all participants on an intention-to-treat basis. External and internal validity of results will be checked using baseline and general descriptive information available for all eligible families; comparing the characteristics of families who completed the study with those who enrolled in the study but did not complete, and those who did not

enrol. Data from each outcome measure will be summarised for each treatment group and descriptive statistics (frequencies, means, medians, 95% CIs) calculated depending on data distribution. The primary comparison immediately post intervention (20 weeks) will be the AMPS and AHA scores. Outcomes between treatment groups will be compared at follow-up using generalised estimating equations (GEEs), with time (0, 20, 40 weeks) and study group (Mitii™, usual care), as well as a time by group interaction as covariables. We will use the Gaussian family, identity link, and an exchangeable correlation structure. Secondary analyses will compare the outcomes between groups for participation (domains of LIFE-H) and QOL (domains of CP-QOL). For dichotomous outcomes we will compare outcomes between-group outcomes using GEEs with the logistic family and logit link. For continuous variables we shall compare using the Gaussian family and identity link (possibly after transformation, depending on the distribution). The magnitude of BOLD changes between groups will be determined using *iBrain*™: ROI will be delineated for each individual primary motor cortex (PM1), SMA, and ipsilateral motor cortex (PM1ipsi) and active voxels in those regions will be counted. These data will be compared for each region over time using GEEs. In subjects where mirror movements did not occur, lateralisation between ipsi- and contralateral PM1 will be assessed to determine the incidence and magnitude of brain reorganisation. For TMS data changes in mean MT to TMS from ipsi and contralateral hemispheres will be analysed in each group at each F/U. The probability of ipsilateral projections appearing as a result of each treatment paradigm will also be analysed. Statistical significance will be at $p<0.05$ with adjustment for multiple comparisons, and all analyses will be intention to treat. Sensitivity analyses using imputation techniques will investigate whether the effect estimates are biased as a consequence of non-ignorable missing data.

DISCUSSION:

Current models of rehabilitation for children with CP are costly, limited by inequity of access and often not provided at sufficient intensity to drive neuroplasticity to improve outcomes. An effective web based multi-modal training that enhances motor and cognitive abilities using virtual trainers is likely to be a cost effective means of delivering therapy. It is also likely to lead to better translation of skills into the community as participants are responsible for their own training in the home environment. This study has the potential to establish a new cost-effective evidence-based therapy accessible equally by urban, rural and remote children and their families. Should our hypotheses be correct, Mitii™ has the potential to revolutionize delivery of intensive rehabilitation to children and adolescents with CP.

Competing Interests: The authors declare they have no competing interests.

Funding: Project grant: Foundation for Children Grant (RB; JZ), Queensland Government Smart Futures PhD Scholarship (SJ), Smart Futures Co-Investment Program Grant (RB; JZ, AS, SR, TC, PS); NHMRC Career Development Fellowship (RB, 1037220), NHMRC TRIP Fellowship (LS, 1036183), APA Scholarship (LM). The funding bodies have not and will not contribute to the study design; the collection,

management, analysis and interpretation of data; the writing of the final reports or the decision to submit findings for publications.

Authors Contributions: RB, JZ, LS, AS and SR are the chief investigators (CIs) who designed and established this research study. The content of the therapy program Mitii™ was developed by the Helene Elsass Centre then adapted and modified in English for the Australian study. LM drafted the first version of this manuscript. All authors have contributed to the writing of the manuscript and have critically reviewed and approved the final version. RB, JZ and LM were responsible for ethics applications and reporting. SR, RC and RB were responsible for the design, implementation, data collection, analysis of the Advanced Brain Imaging studies. RB, JZ, LS, KW, LM and SJ will take lead roles on data management and preparation of publications on the clinical outcomes of the study and RB, SR, RC will take lead roles on the neuroscience publications from the study. TC and PS will lead the economic evaluation and associated publications. KW advised on EF assessments and will advise on their interpretation. QCPRRC is responsible for the coordination, delivery, ethics, outcomes and study publication. The CI's oversee scientific conduct of the trial.

Acknowledgements: Thank you to the staff from the Helene Elsass Centre and The University of Copenhagen who have provided the Mitii™ program, advised on the Mitii™ content and have provided ongoing support to the Mitii™ training.

REFERENCES

1. Rosenbaum P, Paneth N, Leviton A, et al. A report: the definition and classification of cerebral palsy April 2006. *Dev Med Child Neurol Suppl* 2007;**109**:8-14.
2. Odding E, Roebroeck ME, Stam HJ. The epidemiology of cerebral palsy: incidence, impairments and risk factors. *Disabil Rehabil* 2006;**28**:183-91.
3. Access Economics. The Econonic Impact of Cerebral Palsy in Australia in 2007. Canberra, ACT: Access Economics, 2008.
4. Boyd R, Sakzewski L, Ziviani J, et al. INCITE: A randomised trial comparing constraint induced movement therapy and bimanual training in children with congenital hemiplegia. *BMC Neurol* 2010;**10**:4.
5. 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.
6. Sakzewski L, Ziviani J, Abbott DF, et al. Participation outcomes in a randomized trial of 2 models of upper-limb rehabilitation for children with congenital hemiplegia. *Arch Phys Med Rehabil* 2011;**92**:531-9.
7. Boyd R, Abbott D, Badawi N, et al. Use-dependant neuroplasticity in an RCT of constraint induced movement therapy versus bimanual training for children with congenital hemiplegia [abstract]. *Dev Med Child Neurol* 2010;**52**(Suppl 5):11.
8. Foley L, Maddison R. Use of active video games to increase physical activity in children: a (virtual) reality? *Pediatr Exerc Sci* 2010;**22**:7-20.
9. Maher CA, Williams MT, Olds T, et al. Physical and sedentary activity in adolescents with cerebral palsy. *Dev Med Child Neurol* 2007;**49**:450-7.
10. Zwier JN, van Schie PEM, Becher JG, et al. Physical activity in young children with cerebral palsy. *Disabil Rehabil* 2010;**32**:1501-08.
11. Nelson MC, Neumark-Stzainer D, Hannan PJ, et al. Longitudinal and secular trends in physical activity and sedentary behavior during adolescence. *Pediatrics* 2006;**118**:e1627-34.
12. WHO. Health and Development through Physical Activity and Sport. Geneva: WHO, 2003.
13. WHO. International Classification of Functioning, Disability and Health. Geneva, Switzerland: WHO, 2001.
14. Christiansen C, Baum C, Editors. Occupational Therapy – Overcoming Human Performance Deficits. New Jersey: Slack Incorporated, 1991.
15. Van Zelst BR, Miller MD, Russo RN, et al. Activities of daily living in children with hemiplegic cerebral palsy: a cross-sectional evaluation using the Assessment of Motor and Process Skills. *Dev Med Child Neurol* 2006;**48**:723-7.
16. Cusick A, McIntyre S, Novak I, et al. A comparison of goal attainment scaling and the Canadian Occupational Performance Measure for paediatric rehabilitation research. *Pediatr Rehabil* 2006;**9**:149-57.
17. Krebs HI, Fasoli SE, Dipietro L, et al. Motor Learning Characterizes Habilitation of Children With Hemiplegic Cerebral Palsy. *Neurorehabil Neural Repair* 2012
18. Chan RCK, Shum D, Toulopoulou T, et al. Assessment of executive functions: Review of instruments and identification of critical issues. *Arch Clin Neuropsychol* 2008;**23**:201-16.
19. Bodimeade H, Whittingham K, Lloyd O, et al. Executive function in children and adolescents with the congential hemiplegia type of cerebral palsy [Doctor of Psychology]. The University of Queensland, 2011.
20. Bilde PE, Kliim-Due M, Rasmussen B, et al. Individualized, home-based interactive training of cerebral palsy children delivered through the Internet. *BMC Neurol* 2011;**11**:32.
21. Department of Health and Ageing. Australia's Physical Activity Recommendations for 5-12 year olds. Canberra, 2004.
22. Department of Health and Ageing. Australia's Physical Activity Recommendations for 12-18 year olds. Canberra, 2004.
23. Palisano R, Rosenbaum P, Walter S, et al. Development and reliability of a system to classify gross motor function in children with cerebral palsy. *Dev Med Child Neurol* 1997;**39**:214-23.
24. Eliasson AC, Krumlinde-Sundholm L, Rosblad 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.
25. Badawi N, Watson L, Petterson B, et al. What constitutes cerebral palsy? *Dev Med Child Neurol* 1998;**40**:520-7.
26. Loubinoux I, Carel C, Alary F, et al. Within-session and between-session reproducibility of cerebral sensorimotor activation: a test-retest effect evidenced with functional magnetic resonance imaging. *J Cereb Blood Flow Metab* 2001;**21**:592-607.
27. Charles JR, Wolf SL, Schneider JA, et al. Efficacy of a child-friendly form of constraint-induced movement therapy in hemiplegic cerebral palsy: a randomized control trial. *Dev Med Child Neurol* 2006;**48**:635-42.
28. Gordon AM, Schneider JA, Chinnan A, et al. Efficacy of a hand-arm bimanual intensive therapy (HABIT) in children with hemiplegic cerebral palsy: a randomized control trial. *Dev Med Child Neurol* 2007;**49**:830-38.
29. Krageloh-Mann I, Horber V. The role of magnetic resonance imaging in elucidating the pathogenesis of cerebral palsy: a systematic review. *Dev Med Child Neurol* 2007;**49**:144-51.
30. Guzzetta A, Sinclair K, Clarke D, et al. A novel semi-quantitative scale for classification of brain MRI for children with cerebral palsy [abstract]. *Dev Med Child Neurol* 2010;**52**(Suppl 5):74.

31. Palisano RJ, Hanna SE, Rosenbaum PL, et al. Validation of a model of gross motor function for children with cerebral palsy. *Physical Therapy* 2000;**80**:974-85.
32. Morris C, Galuppi BE, Rosenbaum PL. Reliability of family report for the gross motor function classification system. *Dev Med Child Neurol* 2004;**46**:455-60.
33. Morris C, Kurinczuk JJ, Fitzpatrick R, et al. Reliability of the manual ability classification system for children with cerebral palsy. *Dev Med Child Neurol* 2006;**48**:950-53.
34. Crawford JR, Anderson A, Rankin PM, et al. An index-based short-form of the WISC-IV with accompanying analysis of the reliability and abnormality of differences. *Br J Clin Psychol* 2010;**49**:235-58.
35. Wechsler D. Wechsler Intelligence Scale for Children - fourth edition: administration and scoring manual. New York: Psychological Corporation 2004.
36. Lehericy S, Bardinet E, Tremblay L, et al. Motor control in basal ganglia circuits using fMRI and brain atlas approaches. *Cereb cortex* 2006;**16**:149-61.
37. Waites A, Stanislavsky A, Abbott D, et al. The effect of prior cognitive state on resting state networks measured with functional connectivity. *Hum Brain Mapp* 2005;**24**:59-68.
38. Abbott D, Jackson G. iBrain((R)) - Software for analysis and visualisation of functional MR images. *Neuroimage* 2001;**13**:S59-S59.
39. Frackowiak R, Friston K, Frith C, et al. Human Brain Function. 2nd ed. San Diego: Academic Press, 2003.
40. Tournier JD, Calamante F, Connelly A. Robust determination of the fibre orientation distribution in diffusion MRI: Non-negativity constrained super-resolved spherical deconvolution. *Neuroimage* 2007;**35**:1459-72.
41. Tournier JD, Calamante F, Connelly A. MRtrix: Diffusion tractography in crossing fiber regions. *Int J Imaging Syst Technol* 2012;**22**:53-56.
42. Rose S, Guzzetta A, Pannek K, et al. MRI structural connectivity, disruption of primary sensorimotor pathways, and hand function in cerebral palsy. *Brain Connect* 2011;**1**:309-31.
43. Raffelt D, Tournier JD, Rose S, et al. Apparent Fibre Density: a novel measure for the analysis of diffusion-weighted magnetic resonance images. *Neuroimage* 2012;**59**:3976-399.
44. Rose S, Pannek K, Bell C, et al. Direct evidence of intra- and interhemispheric corticomotor network degeneration in amyotrophic lateral sclerosis: an automated MRI structural connectivity study. *Neuroimage* 2012;**59**:2661-9.
45. Rose S, Rowland T, Pannek K, et al. Structural hemispheric asymmetries in the human precentral gyrus hand representation. *Neuroscience* 2012;**210**:211-21.
46. Zalesky A, Fornito A, Bullmore ET. Network-based statistic: identifying differences in brain networks. *Neuroimage* 2010;**53**:1197-207.
47. Rossini PM, Barker AT, Berardelli A, et al. Noninvasive electrical and magnetic stimulation of the brain, spinal-cord and roots - basic principles and procedures for routine clinical-application. Report of an IFCN committee. *Electroencephalogr Clin Neurophysiol* 1994;**91**:79-92.
48. Facchini S, Muellbacher W, Battaglia F, et al. Focal enhancement of motor cortex excitability during motor imagery: a transcranial magnetic stimulation study. *Acta Neurol Scand* 2002;**105**:146-51.
49. Sohn YH, Kaelin-Lang A, Jung HY, et al. Effect of levetiracetam on human corticospinal excitability. *Neurology* 2001;**57**:858-63.
50. Brasil-Neto JP, Cohen LG, Panizza M, et al. Optimal focal transcranial magnetic activation of the human motor cortex: effects of coil orientation, shape of the induced current pulse, and stimulus intensity. *J Clin Neurophysiol* 1992;**9**:132-36.
51. Fisher A, Bray Jones K. Assessment of Motor and Process Skills. Vol. 1. Development, Standardization, and Administration Manual. 7th ed. Forts Collins, CO: Three Star Press, 2010.
52. Krumlinde-Sundholm L, Eliasson A. Development of the Assisting Hand Assessment: a Rasch-built measure intended for children with unilateral upper limb impairments. *Scan J Occup Ther* 2003;**10**:16-26.
53. Holmefur M, Krumlinde-Sundholm L, Eliasson A. Interrater and intrarater reliability of the assisting hand assessment. *Am J Occup Ther* 2007;**61**:79-84.
54. Holmefur M, Aarts P, Hoare B, et al. Retest and alternate forms reliability of the Assisting Hand Assessment [PhD Thesis]. Karolinska Institutet, 2009.
55. Taylor N, Sand PL, Jebsen RH. Evaluation of hand function in children. *Arch Phys Med Rehabil* 1973;**54**:129-35.
56. Eliasson A, Shaw K, Ponten E, et al. Feasibility of a day-camp model of modified constraint induced movement therapy with and without Botulinum Toxin A injections for children with hemiplegia. *Phys Occup Ther Pediatr* 2009;**29**:311-33.
57. Eliasson AC, Krumlinde-Sundholm L, Shaw K, et al. Effects of constraint-induced movement therapy in young children with hemiplegic cerebral palsy: an adapted model. *Dev Med Child Neurol* 2005;**47**:266-75.
58. Hackel ME, Wolfe GA, Bang SM, et al. Changes in hand function in the aging adult as determined by the Jebsen Test of Hand Function. *Phys Ther* 1992;**72**:373-7.
59. Anderson P. Assessment and development of executive function (EF) during childhood. *Child Neuropsychol* 2002;**8**:71-82.

60. Delis DC, Kaplan E, Kramer JH. Delis-Kaplan Executive Function System (D-KEFS) examiner's manual. San Antonio, TX: The Psychological Corporation. 2001.
61. Gioia G, Isquith P, Guy S, et al. Behavior Rating Inventory of Executive Function. Odessa, FL: Psychological Assessment Resources, 2000.
62. Delis DC, Kaplan E, Kramer JH. Delis-Kaplan Executive Function System (D-KEFS) technical manual. San Antonio, Tx: The Psychological Corporation, 2001.
63. Wechsler D. Wechsler Intelligence Scale for Children - fourth edition: technical and interpretative manual. San Antonio, TX: The Psychological Corporation, 2003.
64. Martin NA. Test of Visual Perceptual Skills. 3rd ed. Novato, CA.: Academic Therapy Publications, 2006.
65. Randall M, Johnson L, Reddihough D. The Melbourne Assessment of Unilateral Upper Limb Function Test: Test administration manual. Melbourne: Royal Children's Hospital, 1999.
66. Randall M, Carlin JB, Chondros P, et al. Reliability of the melbourne assessment of unilateral upper limb function. *Dev Med Child Neurol* 2001;**43**:761-67.
67. Verschuren O, Ketelaar M, Takken T, et al. Reliability of hand-held dynamometry and functional strength tests for the lower extremity in children with Cerebral Palsy. *Disabil Rehabil* 2008;**30**:1358-66.
68. Worrell TW, Borchert B, Erner K, et al. Effect of a lateral step-up exercise protocol on quadriceps and lower extremity performance. *J Orthop Sports Phys Ther* 1993;**18**:646-53.
69. Maher CA, Williams MT, Olds TS. The six-minute walk test for children with cerebral palsy. *Int J Rehabil Res* 2008;**31**:185-8.
70. Li AM, Yin J, Au JT, et al. Standard reference for the six-minute-walk test in healthy children aged 7 to 16 years. *Am J Respir Crit Care Med* 2007;**176**:174-80.
71. Evenson KR, Catellier DJ, Gill K, et al. Calibration of two objective measures of physical activity for children. *J Sports Sci* 2008;**26**:1557-65.
72. Capio CM, Sit CH, Abernethy B. Physical activity measurement using MTI (actigraph) among children with cerebral palsy. *Arch Phys Med Rehabil* 2010;**91**:1283-90.
73. Clanchy KM, Tweedy SM, Boyd RN, et al. Validity of accelerometry in ambulatory children and adolescents with cerebral palsy. *Eur J Appl Physiol* 2011;**111**:2951-9.
74. De Vries SI, Van Hirtum HWJEM, Bakker I, et al. Validity and reproducibility of motion sensors in youth: A systematic update. *Med Sci Sports Exerc* 2009;**41**:818-27.
75. Trost SG, Pate RR, Freedson PS, et al. Using objective physical activity measures with youth: How many days of monitoring are needed? *Med Sci Sports Exerc* 2000;**32**:426-31.
76. Janz KF. Validation of the CSA accelerometer for assessing children's physical activity. *Med Sci Sports Exerc* 1994;**26**:369-75.
77. van Ravesteyn NT, Scholtes VA, Becher JG, et al. Measuring mobility limitations in children with cerebral palsy: content and construct validity of a mobility questionnaire (MobQues). *Dev Med Child Neurol* 2010;**52**:e229-35.
78. Van Ravesteyn NT, Dallmeijer AJ, Scholtes VA, et al. Measuring mobility limitations in children with cerebral palsy: interrater and intrarater reliability of a mobility questionnaire (MobQues). *Dev Med Child Neurol* 2010;**52**:194-9.
79. Law M, Baptiste S, Carswell A, et al. The Canadian Occupational Performance Measure. 3rd ed. Ottawa, Ontario: COAT Publications ACE, 1999.
80. Law M, Polatajko H, Pollock N, et al. Pilot testing of the Canadian Occupational Performance Measure: clinical and measurement issues. *Can J Occup Ther* 1994;**61**:191-7.
81. Dedding C, Cardol M, Eyssen I, et al. Validity of the Canadian occupational performance measure: a client-centred outcome measurement. *Clin Rehabil* 2004;**18**:660-67.
82. McColl M, Paterson M, Davies D, et al. Validity and community utility of the Canadian Occupational Performance Measure. *Can J Occup Ther* 2000;**67**:22-30.
83. Lowe K, Novak I, Cusick A. Low-dose/high-concentration localized botulinum toxin A improves upper limb movement and function in children with hemiplegic cerebral palsy. *Dev Med Child Neurol* 2006;**48**:170-75.
84. Wallen M, O'Flaherty SJ, Waugh MCA. Functional outcomes of intramuscular botulinum toxin type A and occupational therapy in the upper limbs of children with cerebral palsy: A randomized controlled trial. *Arch Phys Med Rehabil* 2004;**88**:1-10.
85. Fougeyrollas P, Noreau L, Lepage C. Assessment of Life Habits, Children Long Form. Quebec.: RIPPH/INDCP, 2002.
86. Marincek C, Buhler C, Knops H, et al., eds. The LIFE-H: Assessment of the quality of social participation; 2001 2001; Slovenia.
87. Noreau L, Lepage C, Boissiere L, et al. Social participation in children with cerebral palsy: measurment issues and applications. *Dev Med Child Neurol* 2004;**45**:43-44.
88. Noreau L, Lepage C, Boissiere L, et al. Measuring participation in children with disabilities using the assessment of life habits. *Dev Med Child Neurol* 2007;**49**:666-71.

89. Coster W, Law M, Bedell G, et al. Development of the participation and environment measure for children and youth: conceptual basis. *Disabil Rehabil* 2012;**34**:238-46.

90. Coster W, Bedell G, Law M, et al. Psychometric evaluation of the Participation and Environment Measure for Children and Youth. *Dev Med Child Neurol* 2011;**53**:1030-7.

91. Goodman R. The Strengths and Difficulties Questionnaire: A research note. *J Child Psychol Psychiatry* 1997;**38**:581-86.

92. Goodman R. The extended version of the Strengths and Difficulties Questionnaire as a guide to psychiatric caseness and consequent burden. *J Child Psychol Psychiatry* 1999;**40**:791-99.

93. Goodman R. Psychometric propeties of the Strengths and Difficulties Questionnaire. *J Am Acad Child Adolesc Psychiatry* 2001;**40**:1337-45.

94. Hawes DJ, Dadds MR. Australian data and psychometric propeties of the Strengths and Difficulties Questionnaire. *Aust N Z J Psychiatry* 2004;**38**:644-51.

95. Waters E, Davis E, Boyd R, et al. Cerebral Palsy Quality of Life Questionnaire for Children (CP QOL-Child) Manual. Melbourne: Deakin University, 2006.

96. Davis E, Shelly A, Waters E, et al. Quality of life of adolescents with cerebral palsy: perspectives of adolescents and parents. *Dev Med Child Neurol* 2009;**51**:193-9.

97. Davis E, Waters E, Mackinnon A, et al. Paediatric quality of life instruments: a review of the impact of the conceptual framework on outcomes. *Dev Med Child Neurol* 2006;**48**:311-8.

98. Waters E, Davis E, Mackinnon A, et al. Psychometric properties of the quality of life questionnaire for children with CP. *Dev Med Child Neurol* 2007;**49**:49-55.

99. Davis E, Mackinnon A, Davern M, et al. Description and psychometric properties of the CP QOL-Teen: a quality of life questionnaire for adolescents with cerebral palsy. *Res Dev Disabil* 2013;**34**:344-52.

100. Australian Bureau of Statistics. Census of Population and Housing: Socio-economic Indexes for Areas (SEIFA), 2006. Canberra: ABS, 2008.

Table 1. Tasks and domains trained within the Mitii™ program and the corresponding actions, parameters that can be manipulated by therapists and results received for each task (Please note: Content of Mitii™ is copyright to Mitii™ Development A/S)

Task	Task description	Action	Parameters adjusted	Domains trained	Results displayed
Memory	Memorise a sequence of images	Look at number of images. Images disappear and client must memories them in order which they were shown. Displays sample of images and uses upper limb movement to re-create sequence	Number of images displayed Number of images in sequence Length of time displayed Complexity of images Position of images Number of Repetitions	Upper limb movement Memory/cognition Visual perception	% Correct Time spent on exercise
Brick	Ability to recognise the outline of a picture	Sequence of images displayed, one of which matches shape. Client uses upper limb to drag corresponding image to shape	Number of images Rotation of figures Position of images Position of shape Number of repetitions Complexity of images	Upper limb movement Memory/cognition Visual perception	% Correct Time spent on exercise
Figure builder	Ability to construct a complete image from smaller pieces	An image is in the middle of screen. Small pieces of this and other images are falling down either side. Use upper limb to reach and drag corresponding piece to recreate image from bottom to top.	Number of images Number of pieces Interval between pieces Speed of falling pieces Number of repetitions Complexity of images	Upper limb movement Memory/cognition Visual perception	Number of pieces missed Time spent on exercise
Figure ground	Ability to pick out a figure from an unorganised background	Large background image presented. Use upper limb to pick up small brick and drag to corresponding place in image.	Time held over correct place Precision of placement Number of repetitions Complexity of background	Upper limb movement Visual perception	Time spent on exercise
Spatial relation	Ability to perceive spatial orientation of a figure	Use upper limb to touch the image in the sequence which differs. (Eg. Pear, Apple, Orange, Car. The car is different.)	Number of images Interval between images Time held over correct image Number of repetitions Complexity of images	Upper limb movement Visual perception	% Correct Time spent on exercise
Visual Closure	Ability to recognise an incomplete figure	Series of incomplete images displayed, and complete single image. Use upper limb to drag incomplete image to complete image. Correct image is one that if complete, would be identical to the presented complete image.	Number of images Position of images Internal between images Time held over correct image Repetitions Complexity of images	Upper limb movement Visual perception	% Correct Time spent on exercise

Balloon mathematics	Ability to complete mathematical calculations	Equation and a number of answer options are presented in balloons. Use upper limb to drag pin and pop balloon with correct answer.	Complexity of equation Number of terms in equation Size of number in equation Time held over correct balloon Time equation displayed Time answer displayed Position of balloons Position of pin Number of repetitions	Upper limb movement Memory/cognition Visual perception	% Correct Time spent on exercise
Combination (2-hand exercise)	Ability to co-ordinated both upper limbs	Series of images presented on both sides. Use both hands to drag two matching items into a circle in the centre of the screen	Number of images presented Number of matching pairs Location of goal circle Size of goal circle Time held on correct image Time held in goal circle Number of repetitions Time bomb Complexity of images	Bimanual upper limb coordination Memory/cognition Visual Perception Time challenge	% Correct Time spent on exercise
Flight simulator	Ability to balance against series of lateral displacements	Use band on head to steer the plane against a series of lateral wind gust disturbances	Airplane speed Wind direction Time of wind gust Strength of wind gust Exercise duration	Balance	Time spent on exercise Balance distribution
Follow	Ability to control gross motor movements and activate larger muscle groups	Use band on head to steer an object around screen	Route of object Speed of object movement Amplitude of object movement Size of object Number of repetitions	Lower limb strength Balance	Time spent on exercise % Correct route
Get up/Get down	Activate larger muscle groups to increase intensity and pulse rate	Use band on head to steer object from top to bottom of screen while doing gross motor movement (eg. Sit to stand, Squat to stand, Lunge to stand, Step on/off block)	Location of object Number of repetitions Time bomb	Lower limb strength Balance Time challenge	Time spent on exercise Time per repetition
Follow the leader	Follow a sequence of movements	Video sequence uploaded and client follows visualising themselves and the video in a split screen view	Video created by therapist therefore can modify	Lower limb strength Balance	
UFO	Ability to control gross motor movements and activate larger muscle groups	Use band on head to steer UFO through a series of tunnels. Requires client to squat/extend knees to control	Route of object Speed of object movement Number of repetitions Time bomb	Lower limb strength Balance Time challenge	Time spent on exercise Accuracy of object path

Move	Activate larger muscle groups to increase intensity and pulse rate	Uses large movement of limbs to inflate a balloon until it bursts	Amplitude of movements Movement direction Duration of movement Number of repetitions	Time spent on exercise % increase of balloon
Additional demands				
Balance	Put on wobble board, reduce base of support (e.g. standing on one leg)			
Strength	Step on/off block			

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description	Included in Protocol
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	P1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Prospective registration P4 and p8
	2b	All items from the World Health Organization Trial Registration Data Set	Yes
Protocol version	3	Date and version identifier	1st version for publication
Funding	4	Sources and types of financial, material, and other support	Fully disclosed p27
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Names and affiliations p1 Author contributions p28
	5b	Name and contact information for the trial sponsor	P2
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	The funding bodies and sponsors have no influence on the above items. Disclosed in Funding on P27
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Within author contributions p28
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Background provided p5-7, benefits provided p7
	6b	Explanation for choice of comparators	P7

Objectives	7	Specific objectives or hypotheses	P7-8
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	P9
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	P8
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	P8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	P11
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	The dose of Mitii will be prescribed but controlled by participant therefore self limiting
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	P12
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	P10
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Detailed description of outcomes and their psychometric properties provided
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1 and within study procedure p11

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	P9
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Recruitment described p8 and strategies to achieve sample P9
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	P10
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	P10
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	P10
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	P10
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	P10
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Study instruments described in detail

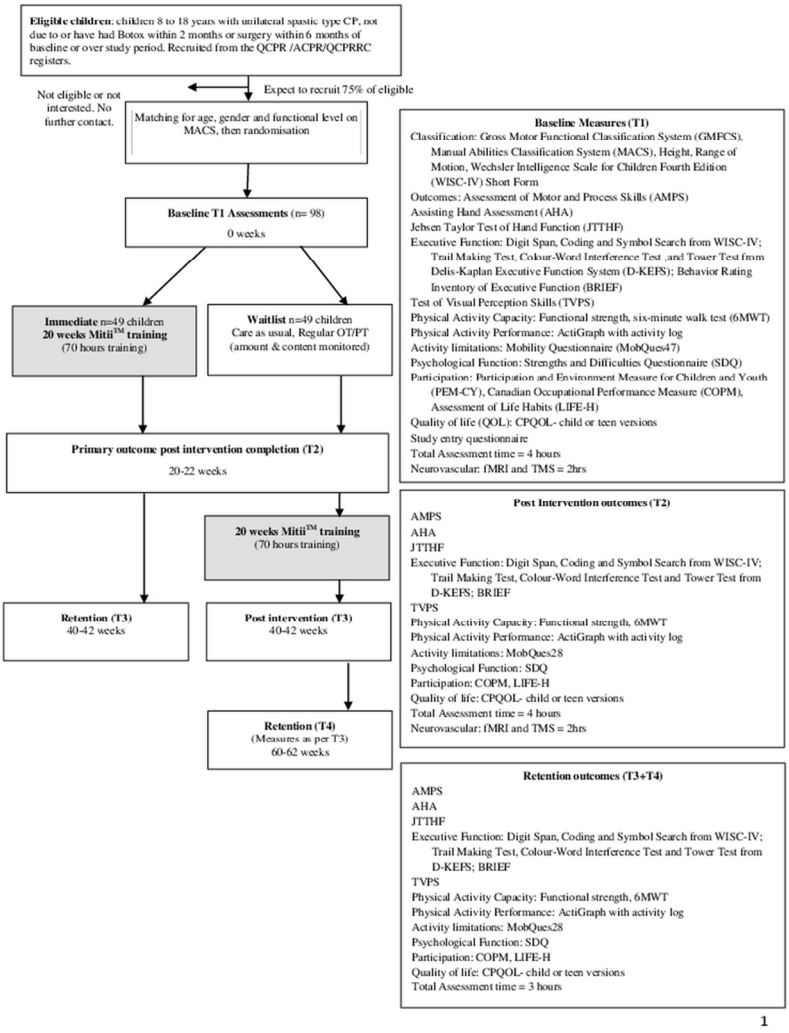
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	P12
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	P12
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	P26
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	P26
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	P12
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	P28
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	P28
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	P10
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	P28
Ethics and dissemination			

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	P8
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	Protocol amendments will be submitted to local ethics committees and trial registration committees, however it is expected that these will not significantly alter the protocol
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	P8
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Personal information and data will be stored in locked fireproof cabinets to be accessed only by study personnel according to our local ethics requirements
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	P28
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	P28
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	Harm from trial unlikely however participants who require travel to attend appointments are provided with travel insurance
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	P4

	31b	Authorship eligibility guidelines and any intended use of professional writers	P28
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Protocol to be published
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Consent form has been approved by local ethics committees
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

Figure 1: CONSORT Flow chart of the Mitii™ cerebral palsy study



CONSORT Flow chart of the Mitii™ cerebral palsy study
90x127mm (300 x 300 DPI)