

# Move it to improve it (Mitii): study protocol of a randomised controlled trial of a novel web-based multimodal training program for children and adolescents with cerebral palsy

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## 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 multimodal programme 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 be matched at baseline and randomly allocated to receive 20 weeks of 30 min of daily Mitii training immediately, or waitlisted for 20 weeks before receiving the same Mitii training (potential total dose=70 h). Outcomes will be assessed at 20 weeks after the start of Mitii, 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

## ARTICLE SUMMARY

### Article focus

- The main aim of this proposed study was to determine if 20 weeks of intensive move it to improve it (Mitii) training can improve upper-limb (UL) activity (unimanual and bimanual), occupational performance and cognitive skills in children and adolescents with CP compared with 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 MRI and transcranial magnetic stimulation to measure central activation in the parts of the brain controlling movement).
- It is hypothesised that Mitii will be more effective than Usual Care (occupational therapists/physiotherapists) for children with congenital hemiplegia (aged 8–18 years) to improve activity (unimanual capacity and bimanual performance) by a mean difference of five points on the Assisting Hand Assessment and 10% decrease in time on the Jebsen-Taylor Test of Hand Function and motor and process skills (Assessment of Motor and Process Skills) will improve by 0.5 logit scores following Mitii intervention.

## 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

## ARTICLE SUMMARY

## 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 multimodal training program consisting of UL 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 of this study

- 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 to test the efficacy of Mitii.

musculoskeletal problems.<sup>1</sup> In Australia, around 600–700 infants are born with CP each year, making it the most common physical disability in childhood.<sup>2</sup> 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 AUD\$43,431 per person with CP per annum.<sup>3</sup> 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 optimise health, function and fitness of individuals with CP to reduce costs associated with the condition.

Several intensive therapy approaches delivered by a therapist directly to the child with CP are currently offered to improve upper limb (UL) function. A systematic review and meta-analysis of all non-surgical UL interventions found some evidence to support these intensive training approaches (eg, 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) randomised 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.<sup>4</sup> Children attended 60 h 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 (3 weeks) with mCIMT yielding greater changes in unimanual capacity at 6 months.<sup>5,6</sup>

In addition to functional changes children receiving mCIMT had greater and earlier use-dependent neuroplasticity, measured with Transcranial Magnetic Stimulation (TMS) immediately postintervention, than those receiving BIM which was sustained at 6 months.<sup>7</sup> These results suggest that a minimum of 60 h 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 h of direct rehabilitation provided by specialist trained occupational therapists (OTs) and/or physiotherapists (PTs). 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 h/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 programmes 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 UL 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.<sup>8</sup> It is known that children and adolescents with CP are less physically active than their typically developing peers<sup>9,10</sup> or compared with children with other physical disabilities, such as spina bifida or head injuries.<sup>11</sup> This is an important health promotion consideration as patterns of physical activity acquired during childhood are more likely to be maintained into adult life, providing the foundation for healthy lifestyle choices.<sup>12</sup> 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),<sup>13</sup> including their impact on physical activity capacity and performance, as well as participation.

Activities of daily living (ADL; ie, life tasks required for self-care and self-maintenance) are fundamental in supporting participation across school, home and community environments.<sup>14</sup> Children and adolescents with unilateral CP often experience difficulties with ADL due to their motor and associated difficulties.<sup>15</sup> Performance of ADL is a high priority for parents/guardians.<sup>16</sup> Therapy targeting ADL for children with unilateral CP often involves task-specific training to stimulate motor learning.<sup>17</sup> Alternatively, therapy may address deficits in motor and cognitive skills that are considered prerequisites for successful performance of ADL. Rehabilitation that involves a combination of UL, gross motor, cognitive and visual perceptual training is likely to improve performance of ADL. 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.<sup>18</sup> Children with mild CP have demonstrated impairments with executive function in multiple domains.<sup>19</sup> 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 multimodal training that enhances cognitive and motor abilities using multidisciplinary 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 multimodal training program comprising UL 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. PTs, OTs 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 individualised programme.

The feasibility of delivering Mitii has been confirmed in a pilot study of nine children achieving on average 35 min of training daily for 20 weeks (total dose 70 h).<sup>20</sup> Compliance was high, with an average of 85% of children meeting or exceeding this dose. In a prepost 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 UL activity (unimanual and bimanual), occupational performance and cognitive skills in children and adolescents with CP compared with 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 MRI (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 ICEF.

The primary hypothesis to be tested is:

1. In a waitlist randomised controlled trial, Mitii will be more effective than Usual Care (OT/PT) for children with congenital hemiplegia (aged 8–18 years) to improve activity (unimanual capacity and bimanual performance) by a mean difference of five 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 (Assessment of Motor and Process Skill, 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 daily life);
4. Psychological functioning (Strengths and Difficulties Questionnaire (SDQ));
5. Participation (Assessment of life habits (LIFE-H)) for categories of personal care, nutrition, education and recreation;
6. Occupational performance (Canadian occupational performance measure (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 (mobility questionnaire-28 (MobQues28));
9. Physical activity capacity immediately following Mitii training (Functional strength: repeated sit to stand, half-kneel to stand and step up tests; and 6 min walk test (6MWT));
10. Physical activity performance (ActiGraph) and greater compliance with the national physical activity recommendations<sup>21 22</sup>;

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 from 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: 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 OTs, PTs 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: (1) Gross Motor Function Classification (GMFCS) I or II<sup>23</sup>; Manual Abilities Classification scale (MACS) I, II, III<sup>24</sup>; (2) aged 8–18 years with sufficient cooperation and cognitive understanding to perform the tasks and (3) able to access the internet at home (phone line or internet access). Children will be excluded if they have (1) received UL or lower-limb surgery in the previous 6 months; (2) unstable epilepsy (ie, frequent seizures not controlled by medication) or (3) 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.<sup>25</sup>

### Sample size

Sample size calculation is based on the primary hypothesis comparison between the functional effects of Mitii compared with standard care at 20 weeks on the AMPS. This study examines a continuous response variable from matched waitlist control and immediate-intervention participants with one waitlist control per immediate-intervention participant. In a previous study of Mitii the

response within each group was normally distributed with SD 0.58 on the AMPS.<sup>20</sup> 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 participants. 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. Participant numbers will allow for some loss of information due to participant refusal (10%) and scans where motion is a confounder (10%). With 40 participants 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 coefficient of variation (CV) for control participants performing motor tasks (CV of 11% in PM1 and 35% in SMA),<sup>26</sup> 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 randomised controlled 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 randomised to either:

1. Immediate intervention group  
Families return home with Mitii equipment and begin training immediately; or
2. Waitlist delayed intervention (control) group  
Families continue care as usual for 20 weeks and then return to Brisbane for 1-day reassessment 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 UL 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 UL the previous 2 months will have assessments and interventions postponed until after their standard follow-up has been completed (usually 6–8 weeks postinjection). All concurrent therapies provided by local services duration, frequency and content will be recorded by questionnaire at 20-week follow-up.

### 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



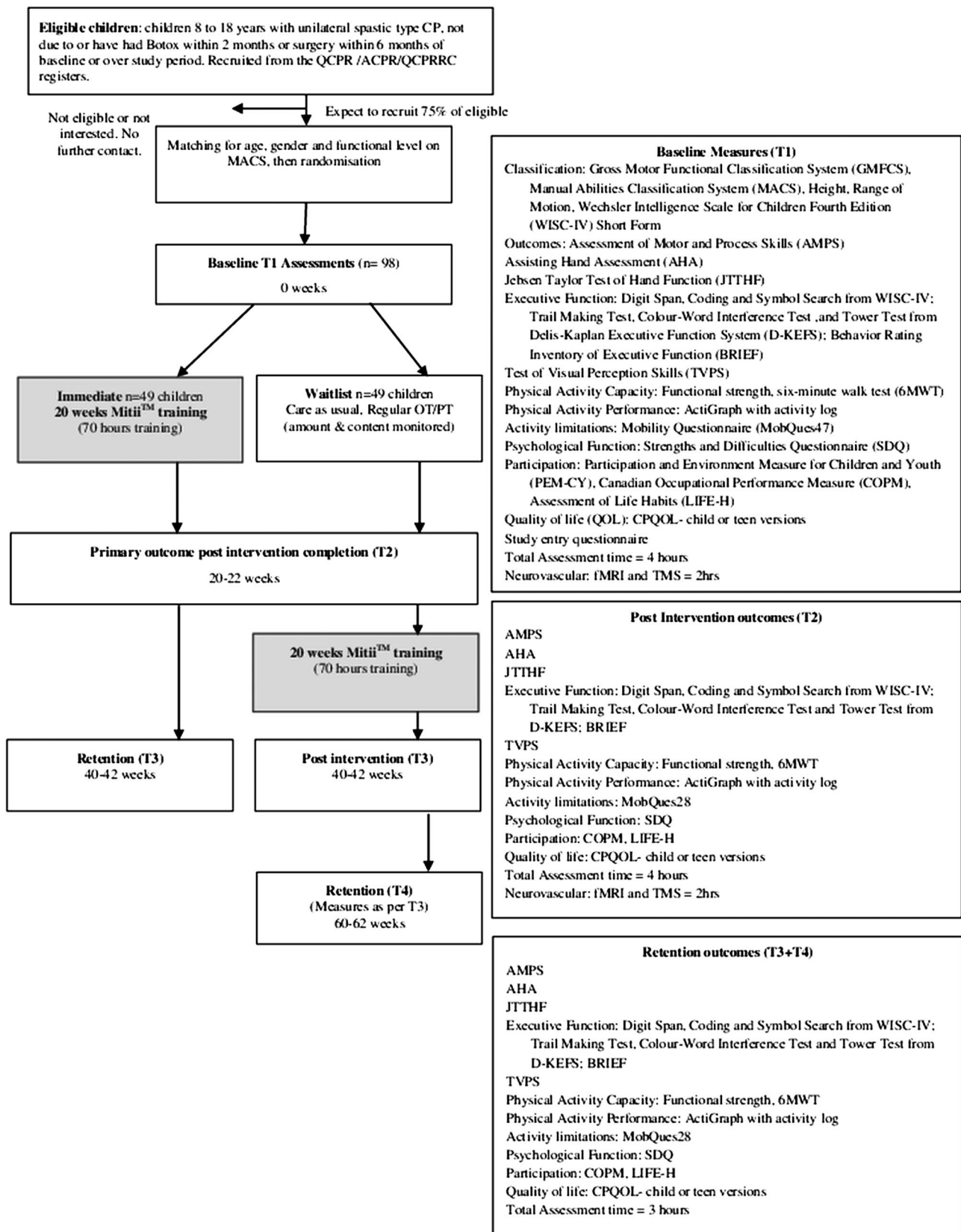


Figure 1 CONSORT flow chart of the move it to improve it (Mitii) cerebral palsy study.

has often been present in rehabilitation studies.<sup>27 28</sup> Once matching has been achieved, children will be randomised within pairs (one member of each pair to be

randomly allocated to each group) from sealed 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 reorganisation. Data on the AHA and Melbourne assessment of unilateral UL function (MUUL) will be rated from video recordings analysed by assessors masked to group allocation and assessment time point.

### Adverse events

Any minor and major event 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 start 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 reassessment 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 postintervention at 20 weeks postrandomisation (T2), and then retention (40-week postrandomisation, T3). For the Waitlist group, an additional baseline assessment will be conducted at 20 weeks postrandomisation (T2), and then postintervention at 20 weeks after commencing the Mitii training (40 weeks postrandomisation, T3). Retention of effects will be collected in the Waitlist group by an additional assessment at 60 weeks postrandomisation (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 (PT, OT and psychologist) to ascertain fine and gross motor skills and cognitive abilities. A deidentified 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 (eg, unilateral and bilateral UL movement, sit-to-stand, balance) as well as cognitive tasks (eg, matching, ordering, moving and tracking objects; see table 1). The combination of UL and lower-limb gross motor, cognitive and visual perceptual training is designed to have a multimodal 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 (ie, mathematical question or similar) and respond with a motor act (ie, 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

Participants log into the Mitii website and access their individualised training programmes at their convenience, enabling training to be completed at any time. The specific content and progression of the programme 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 (eg, increasingly complex forms have to be correctly identified), cognitive (eg, increasingly difficult mathematical questions) or motor challenges (eg, child has to do more repetitions or work with higher load). This is completed by therapists (PT, OT 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 programme of 30-min duration. Mitii should be completed in, at least, 30 min daily for 6 days/week for 20 weeks to provide sufficient training intensity (providing a total dose of 60 h). Tasks can be divided into those training gross-motor or physical activity (eg, repetitive sit-to-stand exercises) or those

**Table 1** Tasks and domains trained within the Mitii programme 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 recreate 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 Interval between images Time held over correct image Repetitions Complexity of images	Upper limb movement Visual perception	% Correct Time spent on exercise

Continued

**Table 1** Continued

Task	Task description	Action	Parameters adjusted	Domains trained	Results displayed
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 (two-hand exercise)	Ability to coordinated 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	

Continued



Table 1 Continued

Task	Task description	Action	Parameters adjusted	Domains trained	Results displayed
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 (eg, standing on one leg)				
Strength	Step on/off block				
Mitii, Move it to improve it.					

combining cognitive or visual perception and an UL task (eg, moving the UL to solve a mathematic equation). To ensure each participant receives a similar training programme, all sequences will comprise approximately 60% cognitive-UL and 40% gross-motor training tasks individualised to the child's abilities. Step blocks and balance foam can be added as the child progresses to add additional challenge to the tasks.

**Participant and data management**

The percentage of eligible participants successfully recruited, and number 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 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 programme 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 programme 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 problems and to support engagement.

**Classification measures**

**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 and hypoxic ischaemic injury<sup>29</sup> and a quantitative system to grade the location, extent and severity of the brain lesions with an asymmetry index.<sup>30</sup>

**Gross motor function classification system**

The gross motor function classification system (GMFCS) classifies the child's ability to carry out self-initiated movements related to sitting and walking across five levels.<sup>23</sup> The GMFCS has strong construct validity with the Gross Motor Function Measure (r=0.91)<sup>31</sup> and good interobserver reliability between professionals and between professionals and parents.<sup>32</sup> In this sample of children with hemiplegia, all children will be GMFCS level I (walks without limitations) and II (walks with limitations).

**Manual abilities classification system**

MACS classifies the child's ability to handle objects in daily activities on one of five levels.<sup>24</sup> 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).<sup>33</sup> 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).

#### Anthropometric data

Height will be measured to the nearest 0.5 cm while the child is standing with the back against a wall.

#### Wechsler Intelligence Scale for Children—fourth edition short form

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 index (VCI), perceptual reasoning index (PRI), Working Memory Index (WMI) and processing speed index (PSI). An overall short form, full-scale intellectual functioning 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 (eg, 'what is a hat'). For Similarities, children will describe how two words that are common objects or represent common concepts are similar (eg, 'in what ways are a cat and a 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 the Symbol Search and the Coding tasks need to be rapidly completed within 2 min. Index scores will be converted into scaled scores in accordance with normative data based on the child's age and gender (mean=100, SD=15).<sup>34 35</sup> All index scores of the WISC-IV SF have shown moderate to high levels of internal consistency ( $\alpha=0.87-0.96$ ) and are equivalent to those documented for the full WISC-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.

#### Whole-brain fMRI 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 with conventional 1.5T scanners which will reduce the time in the scanner and improve the resolution of data collected. Published methods<sup>4</sup> will be utilised 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 with rest), visually cued via instructions projected on a screen, timed with an auditory cue for the rate of movement at 2 Hz. The task and rest periods are 30 s with the activation cycle repeated four times.

Children with sufficient comprehension will also complete a complex motor task as an additional task in the scanner. This task is timing versus sequencing task performed in a block design (two runs of 6 min each), where the participant alternates between a block of single index-finger button-pressing and a block of random sequences of three-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.<sup>36</sup> 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 min of resting-state fMRI will also be collected for analysis of functional connectivity (FC). Tasks performed prior to resting-state fMRI can influence FC.<sup>37</sup> 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, echo-planar imaging (EPI), repetition time=3.0 s, Echo Time (TE)=30 ms, Flip angle=850, Slice thickness=3 mm, FOV=216 mm, 44 slices, 72×72 matrix yielding an in-plane resolution of 3.0 mm×3.0 mm). A single set of T2-weighted anatomical, FLAIR and three-dimensional T1 volumes will also be collected. Functional MRI image processing, analysis and visualisation will be performed using iBrain software<sup>38</sup> and SPM software (Wellcome Department of Imaging Neuroscience, London, UK). Detailed information about preprocessing and postprocessing of the fMRI has been published.<sup>4</sup> 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.<sup>39</sup> Due to heterogeneity in lesion location and size across participants, group analysis of intraparticipant change in activation will be using region of interest with iBrain software.<sup>38</sup>

#### 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/mm<sup>2</sup>, 60 contiguous slices with 2.5 mm thickness covering the whole brain, in-plane resolution 2.35×2.35 mm, acquisition time approximately 10 min). 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.<sup>40 41</sup> An automated technique has been developed to generate whole brain tractograms, from which individual white matter pathways (eg, motor and sensory) can be extracted for statistical analysis.<sup>42</sup>

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 corticomotor 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,<sup>43</sup> 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 sub-cortical 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.<sup>44 45</sup> Network-based statistics<sup>46</sup> 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 reorganisation.

#### Transmagnetic stimulation (TMS)

Transmagnetic stimulation (TMS) (MAGSTIM 200) will be performed on all participants in both groups at baseline then at 20–22 weeks postintervention. The baseline study will be conducted following fMRI to prevent

contamination of fMRI findings by TMS. A figure of eight 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 10 Hz–5 kHz, sweep speed 100 m 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:

#### Motor threshold

Stimulation will start at 30% of maximum output and increase in 5% increments until the MEP is established. Only 1% changes in intensity will then be used to calculate the threshold value. Motor threshold (MT) is defined as the lowest level of stimulus intensity which produced an MEP in the target muscle of peak-to-peak amplitude >100 µV on 50% or more of 10 trials.<sup>47</sup>

#### 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 defined as 100%.<sup>48</sup> MEPs obtained by single-pulse TMS using different randomised stimulus intensities of 110%, 120%, 130% and 140% MT will be expressed as a percentage of the CMAP in order to obtain recruitment curves.<sup>49</sup> An average of 10 peak-to-peak MEPs recorded for each stimulus intensity will be calculated.

For MTs 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, UK). 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.

#### 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, UK). 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 transsynaptically and

preferentially elicits late I-waves.<sup>50</sup> The direction of current induced in the brain will be anterior to posterior.

### Primary outcome measures

#### Assessment of motor and process skills

AMPS is a standardised, criterion-referenced, observational assessment of the motor abilities of people 2 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.<sup>51</sup> For the assessment, the patient selects a minimum of two daily activities (eg, dressing, eating and 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 to 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 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.<sup>51</sup> 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.

#### Assisting hand assessment

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.<sup>52</sup> The test consists of 22 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 intrarater 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 (6-12 years) and an adolescent version is under development (>13 years). 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 vs school kids) is also high (ICC=0.99).<sup>53</sup> The AHA is responsive to change due to UL intervention.<sup>54</sup> Investigation of reliability yielded a smallest detectable difference of 3.89 raw scores for the small kids and 3.65 raw scores for the school kids version.<sup>53</sup> The AHA requires standardised training and certification of raters.<sup>52</sup> The AHA will be scored by

certified raters who will be masked to group allocation and order of assessment.

#### Jebsen-Taylor test of hand function

Activity limitations will be measured for unimanual capacity using the JTTHE.<sup>55</sup> The JTTHE evaluates speed and dexterity in six timed tasks with an individual score for each UL. 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 min to both minimise frustration and allow comparison with similar studies in children with congenital hemiplegia.<sup>27 28 56</sup> JTTHE 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.<sup>27 28 56 57</sup> There is high inter-rater reliability (ICC=0.82-1.0) for each subtest and test-test reliability with five patients and two raters ( $r=0.84-0.85$ ) in an aging adult population.<sup>58</sup> JTTHE has demonstrated good responsiveness to detect change due to interventions that improve UL speed and manipulation.<sup>27</sup>

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

### Body structure and function domain

#### Executive functioning

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

#### 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 (eg, 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 ( $r=0.90$ ).<sup>62</sup>

#### 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 to 16, while in Number-Letter Switching, children will be required to switch back and forth between connecting numbers from 1 to 16 in numerical order and letters from A to P in alphabetical order, also printed on an A3 sheet (eg, '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.<sup>62</sup>

#### *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 possible moves to complete the tower; they can only move one disk at a time and they must not 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 ( $\alpha=0.43-0.84$ ) and adequate test-retest reliability ( $r=0.51$ ).<sup>62</sup>

#### *Digit span (from the WISC-IV)*

Digit Span Backwards is a verbal WMI 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 orally to the children increasing from two digits to eight, and they have to repeat the number string in the reverse order (eg, if '3-7-2' the child should say '2-7-3'). A score of one is given to each string repeated correctly in the 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 ( $\alpha=0.80$ ) and adequate test-retest reliability ( $r=0.74$ ).<sup>63</sup>

#### *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 2 min. 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 ( $\alpha=0.82$ ) and test-retest reliability ( $r=0.81$ ) for Coding has been shown.<sup>63</sup>

#### *Symbol search (from the WISC-IV)*

Information processing will also be assessed using Symbol Search. Children will visually scan for target symbols in groups of five symbols and indicate whether the target symbol is in the group or not by placing a line through the word 'yes' or 'no'. Children will be told to work as fast as they can in 2 min. 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 ( $\alpha=0.79$ ) and a high level of test-retest reliability ( $r=0.80$ ).<sup>63</sup>

#### *Behaviour Rating Inventory of Executive Function*

In addition to cognitive measures of EF, behavioural manifestations of executive functions in daily life will be measured using the BRIEF, an 85-item parent-rated questionnaire. Parents rate items (eg, '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, WMI, plan, organisation of materials and monitor and (2) the meta-cognition 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 SDs above the mean, will be used as the cut-off for abnormal elevations across all scales.<sup>61</sup> The BRIEF has been found to be ecologically valid measure of EF and has been shown to have good internal consistency ( $\alpha=0.80-0.98$ ) and high test-retest reliability on the BRI ( $r=0.92$ ), MCI ( $r=0.88$ ) and the GEC ( $r=0.86$ ).<sup>61</sup>

#### *Test of visual perceptual skills*

The Test of visual perceptual skills-3 (TVPS-3) consists of seven subscales: visual discrimination, visual memory, visual spatial relationships, form constancy, visual sequential memory, figure-ground and visual closure.<sup>64</sup> Performance will be determined by the number of correct answers in each test (maximum 16 in each of seven 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 4-18 years.<sup>64</sup>

#### *Melbourne assessment of unilateral upper limb function*

MUUL measures both UL impairment and quality of UL function.<sup>65</sup> It is designed for children aged 5-15 years with CP and consists of 16 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 intrarater 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).<sup>66</sup> The MUUL also has good internal consistency ( $\alpha=0.96$ ).<sup>66</sup> Construct and content validity for the MUUL was established during test development.<sup>66</sup>

### Lower-limb functional strength

Mitii will focus on training functional strength therefore assessment of Repetition Maximum during functional exercise will be used to assess strength. Functional strength will be tested according to the protocol outline by Verschuren *et al.*<sup>67</sup>

#### Lateral step-up

This is the number of step up repetitions onto a bench during 30 s. 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.<sup>68</sup> 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 cycle completed within 30 s is recorded starting with the right leg for all children. This is then repeated for the left leg.

#### Sit-to-stand

This tests the number of sit-to-stand repetitions that can be achieved within 30 s, 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.

#### Half kneel-to-stand

This is the number of repetitions of half kneel-to-stand that can be completed in 30 s. The child is in half-kneeling position 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 starting with the right leg in front, and then repeated with the left leg in front.

For all tests, children will be given two practice repetitions per extremity prior to formal testing. Between each practice and testing, 30 s rest will be provided. Between tests 180 s (3 min) 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 s and will be verbally encouraged.

Acceptable intertester reliability has been demonstrated for functional strength testing in 25 children with CP ((ICC>0.91; 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=0.93–0.96). Mean repetitions for the lateral step up were 13.2 (SD=10.5; SE 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.<sup>67</sup>

#### Six-minute walk test

The 6MWT is a simple, submaximal clinical exercise test which measures the distance walked (6MWD) under controlled conditions over 6 min. The 6MWT has been found to be reliable in independently ambulant adolescents with CP.<sup>69</sup> In this population, test-retest reliability was excellent (ICC=0.98). Percentile curves for the 6MWT have been created, though these were from 1445 typically developing Chinese children aged 7–16 years.<sup>70</sup> No reference curves for children and adolescents with CP exist. While children with CP may exhibit lower 6MWD compared with 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 standardised verbal encouragement asking the children to walk as fast as possible along a flat, straight, 10 m corridor with cones marking the turn-around at each end as per Maher *et al.*<sup>69</sup>

#### Passive range of motion

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

### Activity domain

#### Habitual physical activity

Habitual physical activity (HPA) will be measured using ActiGraph GT3X+ tri-axial accelerometer (Pensacola, Florida, USA). 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 h/day. Analysis will convert counts to activity

intensity using Evenson cut points<sup>71</sup> to allow comparison to the national physical activity guidelines.<sup>21–22</sup> 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.<sup>72</sup> It has also demonstrated excellent classification accuracy, and Evenson cut points were found to be the most accurate for adolescents with CP.<sup>73</sup> 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).<sup>74</sup> Seasonal variation has been demonstrated with less activity being performed in the winter months (ICC=0.54).<sup>74</sup> 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.<sup>75</sup> Acceptable reliability has been found with 4 days of monitoring ( $r=0.75–0.78$ ).<sup>76</sup> 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 min period and then conduct selected light, moderate and vigorous assessment tasks, interspersed with 5 min rest periods in a standardised manner while 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 the Mitii training 2-day visit.

### Mobility questionnaire

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 daily 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 0–100 (with a low score representing severe limitations in mobility):  $\text{MobQues47}=(\sum \text{item}/188)\cdot 100$ ;  $\text{MobQues28}=(\sum \text{item}/112)\cdot 100$ . 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 ‘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,  $r=0.67$ ,  $p<0.001$ ).<sup>77</sup> It has also been demonstrated to be a reliable instrument.<sup>78</sup> For the strong inter-rater reliability was found for the MobQues47 (ICC=0.92) and MobQues28 (ICC=0.87). The SEM was 7.8 and 8.9, respectively. As expected, the intrarater reliability was higher for both MobQues versions (ICC=0.96–0.99; SEM=3.5–4.9).<sup>78</sup> 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

#### Canadian occupational performance measure

Individualised goals will be measured using the COPM to evaluate self-perception of occupational performance over time.<sup>79–80</sup> COPM will be administered by one OT with the child/adolescent and parent. 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 of 1–10. An average score for performance and satisfaction is calculated.<sup>67</sup> 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).<sup>80–82</sup> The COPM has demonstrated responsiveness to change in paediatric clinical trials,<sup>83–84</sup> and a two-point change on COPM performance has been reported as being clinically significant.<sup>79</sup>

### Assessment of life habits

The LIFE-H is designed for children aged 5–13 years and measures life habits in home, school and neighbourhood environments.<sup>85–86</sup> It is a questionnaire completed by the parent/caregiver about the child. The child version is based on an adult version. The longer version consists of 197 items divided into 12 categories and includes regular activities (eg, 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.<sup>85–87</sup> Adequate to excellent internal consistency ( $\alpha=0.73$ – $0.90$  for categories,  $0.97$  for daily activities and  $0.90$  for social roles), intrarater (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.<sup>88</sup> Four categories will be evaluated in this study including nutrition (eg, mealtime activities), personal care (eg, 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 programme.

#### Participation and environment measure for children and youth

Participation and environment measure for children and youth (PEM-CY) is a newly developed, parent-report measure for children aged 5–17 years that examines participation and environment across three settings: home, school and community.<sup>89</sup> 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 youth participate in important activities within the home, school and community environments and the extent to which particular features of these environments are perceived to support or challenge the youth's participation. Evidence of the psychometric properties of this new instrument are limited to date, however data from a sample of 576 youth showed internal consistency was moderate to good ( $\alpha>0.59$ ) across the scales. Test–retest reliability was moderate-to-good (ICC $>0.58$ ) across a 1-week to 4-week period using the online version of the assessment.<sup>90</sup> The PEM-CY will be collected at baseline.

#### Strengths and Difficulties Questionnaire

The SDQ will be used to measure parents' perceptions of prosocial and difficult behaviours in their child.<sup>91–92</sup> The SDQ has a total of 33 items. The first 25 items are divided into five scales and assess the frequency of emotional symptoms, conduct problems, inattention/hyperactivity, peer problems and prosocial behaviour (eg, 'considerate of other people's feelings'). These items are rated upon reflection of the last 6 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 difficulty score (0–40) will be calculated, with higher scores indicating more distress on all scales except prosocial behaviour. A clinical cut-off of  $\geq 17$  will be utilised on the total difficulties score. The total score on the five scales and the overall total difficulties score will be utilised as measures of the child's psychological functioning. Moderate to high internal consistency ( $\alpha=0.73$ – $0.82$ ) and test–retest

reliability ( $r=0.77$ – $0.85$ ) has been shown on the overall total difficulties score.<sup>93–94</sup>

#### Cerebral palsy quality of life

QOL will be measured using a condition specific measure, either the cerebral palsy QOL (CPQOL)-Child parent report,<sup>95</sup> or for children 9 years or age or older, the CPQOL-Teen.<sup>96</sup> Results of factor analysis demonstrated that the CPQOL measures seven broad domains of QOL: social well-being and acceptance, functioning, participation, physical health, emotional well-being, access to services, pain, impact of disability and family health. The psychometric properties of the CPQOL-Child are excellent, with strong internal consistency ( $\alpha=0.74$ – $0.92$  for parent-proxy report;  $\alpha=0.80$ – $0.90$  for child self-report). Test–retest is adequate (ICC= $0.76$ – $0.89$ ) and it is moderately correlated with generic QOL and health ( $r=0.30$ – $0.51$ ).<sup>97–98</sup> The CPQOL-Teen, for adolescents aged 13–18 years has strong psychometric properties, with strong internal consistency ( $\alpha=0.81$ – $0.95$  for the primary caregiver report;  $\alpha=0.84$ – $0.96$  for the adolescent self-report) and strong test–retest 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 ( $r=0.40$ – $0.46$ ) and adolescent report ( $r=0.58$ – $0.68$ ) were correlated with a generic QOL instrument.<sup>99</sup>

#### 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 will be 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.<sup>100</sup> Deciles will be reported on a continuum with lower scores reflecting greater socioeconomic disadvantage and higher scores reflecting socioeconomic 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 (eg, medical care, allied health visits and diagnostic/investigational services will be assigned a cost according to a fee schedule and medications will be priced 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 QOL from baseline to end of



intervention based on the CPQOL. 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 (ie,  $(\text{cost}_{\text{Mitii}} - \text{cost}_{\text{usual care}}) / (\text{outcome}_{\text{Mitii}} - \text{outcome}_{\text{usual care}})$ ) 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 postintervention (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 and 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 participants where mirror movements did not occur, lateralisation between ipsilateral 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 ipsilateral 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 multimodal 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 revolutionise delivery of intensive rehabilitation to children and adolescents with CP.

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for the coordination, delivery, ethics, outcomes and study publication. The CI's oversee scientific conduct of the trial.

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