13_CONCORSO PUBBLICO, PER TITOLI ED ESAMI, PER LA COPERTURA A TEMPO DETERMINATO, DELLA DURATA DI CINQUE ANNI PER N. 1 POSTO DI COLLABORATORE PROFESSIONALE DI RICERCA SANITARIA - CAT. D, DA ASSEGNARE ALLA UOC NEUROLOGIA DELLO SVILUPPO

PROVA I

1. NELL'AMBITO DEL TRATTAMENTO RIABILITATIVO DEL BAMBINO CON PARALISI CEREBRALE INFANTILE, DEFINIRE L'APPROCCIO SECONDO LA PRASSI DELL'APPRENDIMENTO MOTORIO GIOCO GUIDATO:
   - QUAL È IL MODELLO TEORICO DI CONTROLLO E APPRENDIMENTO MOTORIO SU CUI SI BASA?
   - QUALI SONO I LIVELLI DI INTERVENTO INDIVIDUATI?
   - QUAL È IL RUOLO DEL TERAPISTA?

   IN UN BAMBINO CON TETRAPARESI DISTONICA QUALI STRUMENTI DI VALUTAZIONE UTILIZZI? QUALI SONO GLI OBIETTIVI GENERALI E LE MODALITA' DEL TRATTAMENTO RIABILITATIVO?

2. IN INFORMATICA COSA SI INTENDE PER BIT?
   a. L'UNITÀ DI MISURA ELEMENTARE DELL'INFORMAZIONE
   b. L'UNITÀ DI MISURA DELLA VELOCITÀ DI ELABORAZIONE DI UN COMPUTER
   c. L'UNITÀ DI MISURA DELLA CAPACITÀ DI CALCOLO DELLA MEMORIA

3. LEGGA E TRADUCA IL TESTO ALLEGATO TRATTO DALLA LETTERATURA SCIENTIFICA

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PEDIATRIC NEUROLOGY (WE KAUFMANN, SECTION EDITOR)

State of the Evidence Traffic Lights 2019: Systematic Review of Interventions for Preventing and Treating Children with Cerebral Palsy

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Abstract

Purpose of Review Cerebral palsy is the most common physical disability of childhood, but the rate is falling, and severity is lessening. We conducted a systematic overview of best available evidence (2012–2019), appraising evidence using GRADE and the Evidence Alert Traffic Light System and then aggregated the new findings with our previous 2013 findings. This article summarizes the best available evidence interventions for preventing and managing cerebral palsy in 2019.

Recent Findings Effective prevention strategies include antenatal corticosteroids, magnesium sulfate, caffeine, and neonatal hypothermia. Effective allied health interventions include acceptance and commitment therapy, action observations, bimanual training, casting, constraint-induced movement therapy, environmental enrichment, fitness training, goal-directed training, hippotherapy, home programs, literacy interventions, mobility training, oral sensorimotor, oral sensorimotor plus electrical stimulation, pressure care, stepping stones triple P, strength training, task-specific training, treadmill training, partial body weight support treadmill training, and weight-bearing. Effective medical and surgical interventions include anti-convulsants, bisphosphonates, botulinum toxin, botulinum toxin plus occupational therapy, botulinum toxin plus casting, diazepam, dentistry, hip surveillance, intrathecal baclofen, scoliosis correction, selective dorsal rhizotomy, and umbilical cord blood cell therapy.

Summary We have provided guidance about what works and what does not to inform decision-making, and highlighted areas for more research.

Keywords Cerebral palsy · Systematic review · Traffic light system · Evidence based · GRADE

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Introduction

Cerebral palsy is the most common physical disability of childhood. In the last decade, major discoveries have been made in early diagnosis, prevention, and treatment, altering incidence, prognosis, and treatment responsivity. In high-income countries such as Australia, motor severity has lessened and the incidence of cerebral palsy has fallen by a staggering 30% [1]. Non-ambulant forms of cerebral palsy, co-occurring epilepsy, and co-occurring intellectual disability are less frequent, meaning more children than ever before can walk [2]. Epidemiologists propose that the reduction in incidence and severity is likely due to a combination of comprehensive obstetric and neonatal intensive care interventions.

In recent years, the cerebral palsy treatment evidence base has continued to expand rapidly, providing clinicians and families with the possibility of newer, safer, and more effective interventions. Since we last provided a comprehensive summary of the cerebral palsy intervention evidence in 2013, another 200+ systematic reviews have been published [3•]. This increasing volume of research evidence makes keeping up-to-date challenging for busy clinicians and overwhelming for families. Furthermore, the introduction of new interventions extends what clinicians need to know to allow sound clinical reasoning and decision-making [4].

This paper aimed to systematically describe the best available evidence for cerebral palsy interventions in 2019. We searched for the best available evidence published after 2012 and aggregated the new findings with our previous 2013 summary of evidence, using the updated GRADE system and the Evidence Alert Traffic Light System [5, 6]. The purpose of the paper was to describe what treatments have demonstrated evidence and highlight areas for more research. We rated the whole cerebral palsy intervention evidence base within the one paper to provide families, clinicians, managers, and policy makers with a helicopter view of best available intervention evidence to (a) inform decision-making by succinctly describing effective, emergent, and ineffective care; (b) aid comparative clinical decision-making about alike interventions and indications; and (c) provide a comprehensive resource to aid the creation of knowledge translation tools to promote evidence implementation.

Methods

Study Design

We conducted a systematic overview of best available evidence using the systematic review of systematic reviews methodology in order to provide an overview of the current state of the evidence [7].

Search Strategy

Our review was carried out using a protocol based upon recommendations from the Cochrane Collaboration and reported according to the PRISMA statement [8, 9••]. Relevant articles were identified by searching: CINAHL (2012 to 2019); Cochrane Database of Systematic Reviews [www.cochrane.org]; EMBASE (2012 to 2019); ERIC (2012 to 2019); PubMED (2012 to 2019), PsycINFO (2012 to 2019), MEDLINE (2012 to 2019), OTSeeker [www.otseeker.com]; Physiotherapy Evidence Database (PEDro) [www.pedro.fhs.usyd.edu.au]; Psychological database for Brain Impairment Treatment Efficacy (PsycBITE) [www.psycbite.com]; PsycINFO (1935 to 2012); PubMED; and Speech Pathology Database for Best Interventions and Treatment Efficacy (speechBITE) [www.speechbite.com]. We sought to update and amalgamate the findings of our 2013 original paper [3•]. Searches were supplemented by hand searching. The search was performed in March–July 2019. Search terms for investigation replicated the same search strategy as our original paper and were supplemented by contributing authors' knowledge of the field, e.g., names of new interventions published since 2012 to add to the search. We also searched for the intervention evidence about preventative treatments in the obstetric or neonatal period, given the considerable reduction in the incidence of cerebral palsy since our last publication.

Electronic databases were searched with OVID host software using PICOs search terms. The full search strategy is available from the authors on request.

Inclusion Criteria

Published studies about interventions for children with cerebral palsy or at risk of cerebral palsy fulfilling the following criteria were included:

Type of Study

First, systematic reviews were preferentially sought [10]. Where multiple systematic reviews existed and newer evidence superseded the findings of earlier evidence, GRADEs were assigned based on the most recent high-quality evidence. We also searched for randomized controlled trials published after the latest systematic review, to account for new trials that might increase our confidence in the estimate of the treatment effect. For interventions where no systematic reviews existed, randomized controlled trials were preferentially sought, and where no randomized controlled trials existed, lower levels of evidence were included and appraised. New data (2012–2019) was then aggregated together with our data published in 2013 in order to review the entire evidence base. Second, retrieved bodies of evidence were appraised using the GRADE and

Evidence Alert Traffic Light System using two independent raters, with unanimous agreement. GRADE is the evidence rating system endorsed by the World Health Organization [5, 6]. GRADE rates both (1) the *quality* of the evidence on a 4-point continuum of High–Moderate–Low–Very Low. Randomized trials start at a score of 4/4 (High) and can be downgraded based on methodological flaws; observational studies start at a score of 2/4 (Low) but can be upgraded based on methodological strengths or downgraded if methodological flaws exist; and (2) the *strength of the recommendation* for use, which weighs up the balance between the benefits and harms, the resource usage' cost effectiveness, health equity, acceptability to consumers, and implementation feasibility [5]. When available, published outcomes of benefits were used to inform the strength of the recommendation. If no published literature was available, expert opinion was used. Recommendations were developed by the panel using the GRADE updated Evidence to Decision framework [5]. The Evidence Alert Traffic Light System was also applied to assist clinicians in obtaining clear, clinically useful answers within minutes [6]. The Evidence Alert uses a three-level traffic light color coding that recommends a course of action for implementation of the evidence within clinical practice. Green means go, because high-quality evidence from RCTs and systematic reviews indicates intervention effectiveness. Red means stop, because high-quality evidence from RCTs and systematic reviews indicates ineffectiveness or harm. Yellow means measure clinical outcomes, because either (i) promising evidence suggests possible effectiveness, but more research would increase our confidence in the estimate of the effect; or (ii) no research exists and therefore effects are unknown; or (iii) conflicting findings exists and therefore it is unclear how a patient might respond.

Types of Intervention

Studies that involved the provision of intervention either by a medical practitioner, an allied health professional, or an alternative and complementary medicine practitioner.

Types of Participants

Studies that explicitly involved human subjects. In the cerebral palsy preventative treatments evidence base, the participants were pregnant mothers or neonates. In the intervention evidence base, the participants were children living with cerebral palsy, in which > 25% of the participants had a diagnosis of cerebral palsy. We used a low cut off because many allied health interventions are provided using the exact same approach across multiple diagnostic groups (e.g., dysphagia management for stroke, brain injury, and cerebral palsy). We did not want to overlook important evidence that had been shown feasible and efficacious in the cerebral palsy population that was published within mixed population studies.

Studies were excluded from the review if (a) they were diagnostic, prognostic, or instrumentation studies; (b) they had lower levels of evidence, unless no systematic review or clinical trial had been published; (c) participants were adults; (d) they reviewed generic preventative interventions, e.g., good parenting; (e) they reviewed an entire discipline (e.g., physiotherapy, occupational therapy, speech pathology) and did not specify or sub-analyze individual named interventions but rather aggregated them together; (f) a second publication of the same study published the same results or participants; and/or (g) studies were unpublished or non-peer reviewed.

Data Abstraction

A data abstraction sheet based on the Cochrane's recommendations was used [8]. Abstracts identified from searches were screened by two independent raters to determine eligibility for further review. Abstracts were retained for full review if they met the inclusion criteria or if more information was required from the full-text to confirm the study met all eligibility criteria. Two independent reviewers then reviewed full-text versions of all retained articles and all additional articles identified by hand searching. Full-text articles were retained if they met inclusion criteria. Agreement on inclusion and exclusion assignment of the full-text articles was unanimous. Data extracted from included studies comprised citations, domains of impact of the intervention, level of the International Classification of Disability and Function (ICF) the intervention was aimed at, participants, study design, and dose. All the data required to answer the study questions were published within the papers, so no contact with authors was necessary.

Ethics and Registration

The study did not involve contact with humans, so the need for ethical approval was waived by the Cerebral Palsy Alliance's Human Research Ethics Committee. This systematic review was not registered.

Results

One thousand five hundred eighty-four citations were identified using the search strategy, of which 247 articles met the inclusion criteria for review [9••, 10, 11••, 12–248]. The study flow is summarized in the PRISMA diagram (Fig. 1) [249].

We identified 182 interventions using our search strategy, an increase of 118 interventions from our 2013 review. Of these interventions, 41/182 (23%) were strategies aiming to prevent cerebral palsy and 141/182 (77%) were interventions aiming to manage cerebral palsy. The prevention strategies

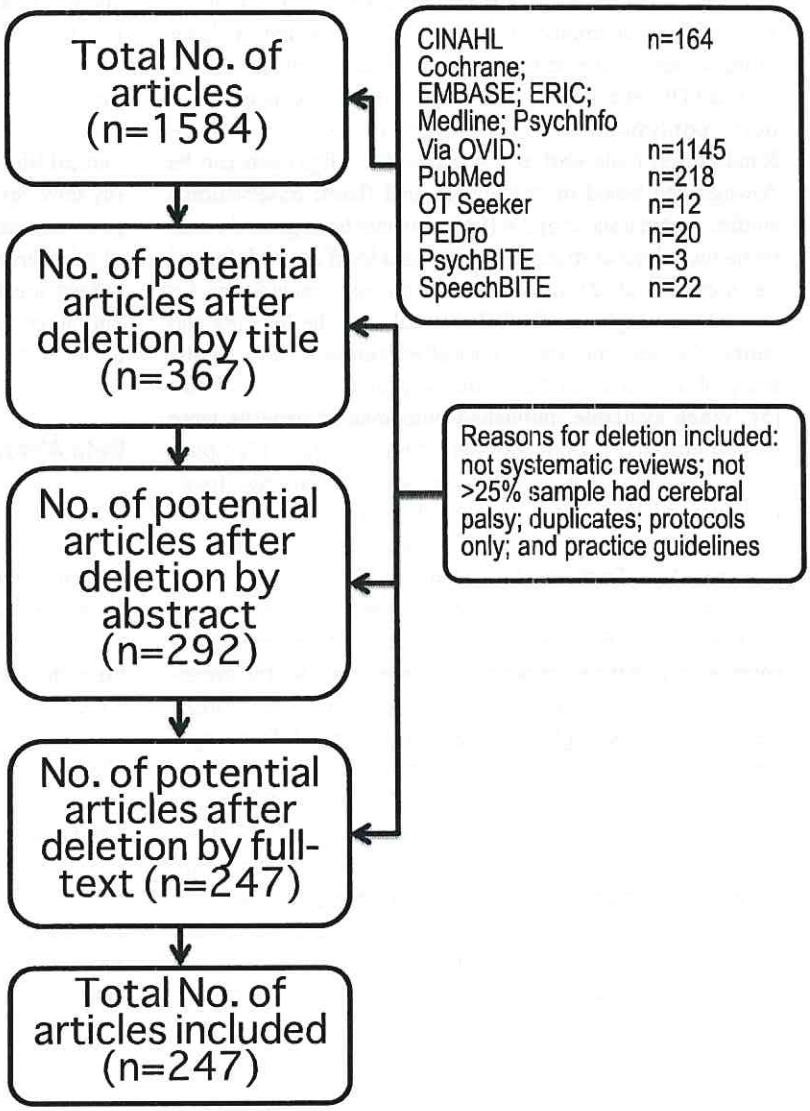

Fig. 1 Flow diagram of included articles

were categorized into antenatal prevention strategies (11/41, 27%) and neonatal prevention strategies (30/41, 73%). The interventions were categorized into allied heath interventions (83/141, 59%), pharmacological interventions (25/141, 18%), surgical interventions (19/141, 13%), regenerative medicine interventions (4/141, 3%), and complementary and alternative medicine (10/141, 7%). From these 182 interventions, we identified 393 intervention outcome indicators that had been studied in children with cerebral palsy. In five indications, two separate gradings were assigned, because the quality of the evidence was different in two sub-populations (e.g., ambulant versus non-ambulant) for the same intervention aim. This took the GRADE count by indication to a total of 398 indications.

Some of the included systematic reviews had already conducted quality ratings on the body of evidence using the GRADE system. As per the GRADE process, we confirmed whether or not we agreed with these findings and also carried out assignment of GRADE coding for all other included papers. Across the 398 intervention outcomes, the GRADE ratings were as follows: 14% of outcomes assessed (54/398) were graded "do it" (i.e., Green light, go interventions); 66% (264/398) were graded "probably do it" (i.e., Yellow light, weak positive); 17% (68/398) were graded "probably don't do it" (i.e., Yellow light, weak negative); and 3% ($n = 12/398$) were graded "don't do it" (i.e., Red light, stop interventions).

Each intervention was coded using the ICF by the intervention's desired outcome. Out of the 383 intervention outcomes for children with CP identified in this study, $n = 241/383$ (62%) were aimed at the body structures and function level; $n = 49/383$ (13%) were aimed at the activity level; $n = 12/383$ (3%) were aimed at the participation level; $n = 11/383$ (3%) were aimed at the environmental factors level; $n = 1/383$ (< 1%) were aimed at the personal factors level; $n = 58/383$

(15%) were aimed at a combined body structures and activities level; and $n = 11/383$ (3%) were aimed at a combined activities and participation level.

Participants

This study included participants with cerebral palsy, a complex and heterogeneous condition. We included studies involving any motor sub-type [spastic, dyskinetic, or ataxic], any topography [hemiplegic/unilateral, diplegic/bilateral, or quadriplegic/bilateral], and any functional ability level [Gross Motor Function Classification System (GMFCS) levels I–V and Manual Ability Classification System (MACS) levels I–V [250, 251]]. In the detailed supplementary extraction table (Online Resource, Table 1), we noted which interventions had been tested in the various sub-groups and severities.

The main results are detailed in the online table, which outlines the citation, the name of the intervention, the intervention indicator, the types of participants the intervention had been tested on, the dose/intensity used within the research studies, the GRADE ratings, the panels reflections on the evidence to decision recommendation process, and the clinical nuance of findings and considerations for interpretation. We strongly urge readers to read the detailed online resource to gain the necessary specifics for understanding the evidence base.

To provide a summary of the online table and to assist with comparative clinical decision-making amongst intervention options for the same desired outcome, we mapped the interventions that seek to provide analogous outcomes, using bubble charts. In the bubble charts, the name of the circle is the intervention, and the italics under the title is the outcome measured and obtained. The size of the circle correlates to the volume of published evidence. The circle size was calculated by the amount and quality of evidence published. Bubble size 1, observational studies (OBS) only; size 2, 1–3 RCTs; size 3, 4–15 RCTs; and size 4, 15+ RCTs. The location of the circle on the *y*-axis of the graph corresponds to the GRADE system rating and estimate of effect (i.e., no effect was placed close to the worth it line, whereas a large treatment effect was placed further away from the worth it line). The color of the circle correlates to the Evidence Alert System (Fig. 2).

Discussion

High levels of evidence exist in the literature summarizing effective preventive strategies and intervention options for children with cerebral palsy. There was an exponential increase in the number of systematic reviews and clinical trials published about cerebral palsy interventions since our last review. We observed a substantial increase in the number of systematic reviews published about acupuncture, pharmacological agents for managing tone, orthopedic surgery, dysphagia management, physical activity, participation, and clinical trials in regenerative medicine.

Prevention of Cerebral Palsy

Undoubtedly, the most notable breakthroughs in the field of cerebral palsy research in the last decade have been made in the area of prevention [9••, 10, 11••, 12–18]. The rate of cerebral palsy has fallen by 30% in some high-income countries, bringing the prevalence down to 1.4 per 1000 [1, 2]. Babies born preterm constitute 43% of all cerebral palsy [2]. Antenatal magnesium sulfate before delivery of an infant less than 30 weeks' gestation prevents 30% of cerebral palsy (green light) [9]. Antenatal corticosteroids decrease intracranial hemorrhage and thereby also act as an effective neuroprotectant (green light) and have become the standard of care [9]. More research would increase our confidence in the estimate of the effect, but further trials are not feasible as it would be unethical to withhold antenatal corticosteroids in premature birth. Once an infant is born preterm and is mechanically ventilated, prophylactic caffeine (methylxanthines) prior to extubation effectively prevents cerebral palsy (green light) [11••]. For babies born at term with neonatal encephalopathy or asphyxia, therapeutic hypothermia commenced within 6-h of delivery is neuroprotective and prevents 15% of cerebral palsy associated with intrapartum hypoxia (green light) [11••]. There is now a pressing ethical imperative to translate prevention breakthroughs and a range of public health initiatives from high-income countries to low-income and middle-income countries, where the disease burden is high [252]. For example, in Bangladesh, the rate of cerebral palsy is more than double that of Australia (3.4 versus 1.4 per 1000). Twice as many Bangladeshi children have severe motor impairments (GMFCS IV–V = 43.6%, compared with 26% in Australia), and 78.2% do not receive any rehabilitation [252]. Delayed umbilical cord clamping is also under investigation. As yet there is no specific data pertaining to whether delayed clamping prevents cerebral palsy, but we anticipate this will change in the near future and clinicians should stay abreast of this evidence base.

In recent years, our understanding of the genetic basis for cerebral palsy has advanced substantially [253]. A genetic contribution is likely in one-third of all children with cerebral palsy, especially in those without traditional risk factors such as prematurity and hypoxia [253]. As our understanding of neurobiology and genomics expands, the revolutionized field will result in the development of new prevention and treatment targets [253]. Experts also predict that future neuroprotective interventions will take advantage of trimester-specific brain development knowledge and that development of novel treatments will be informed by advances in biomarkers of brain injury, genetics, and neuroimaging [254].

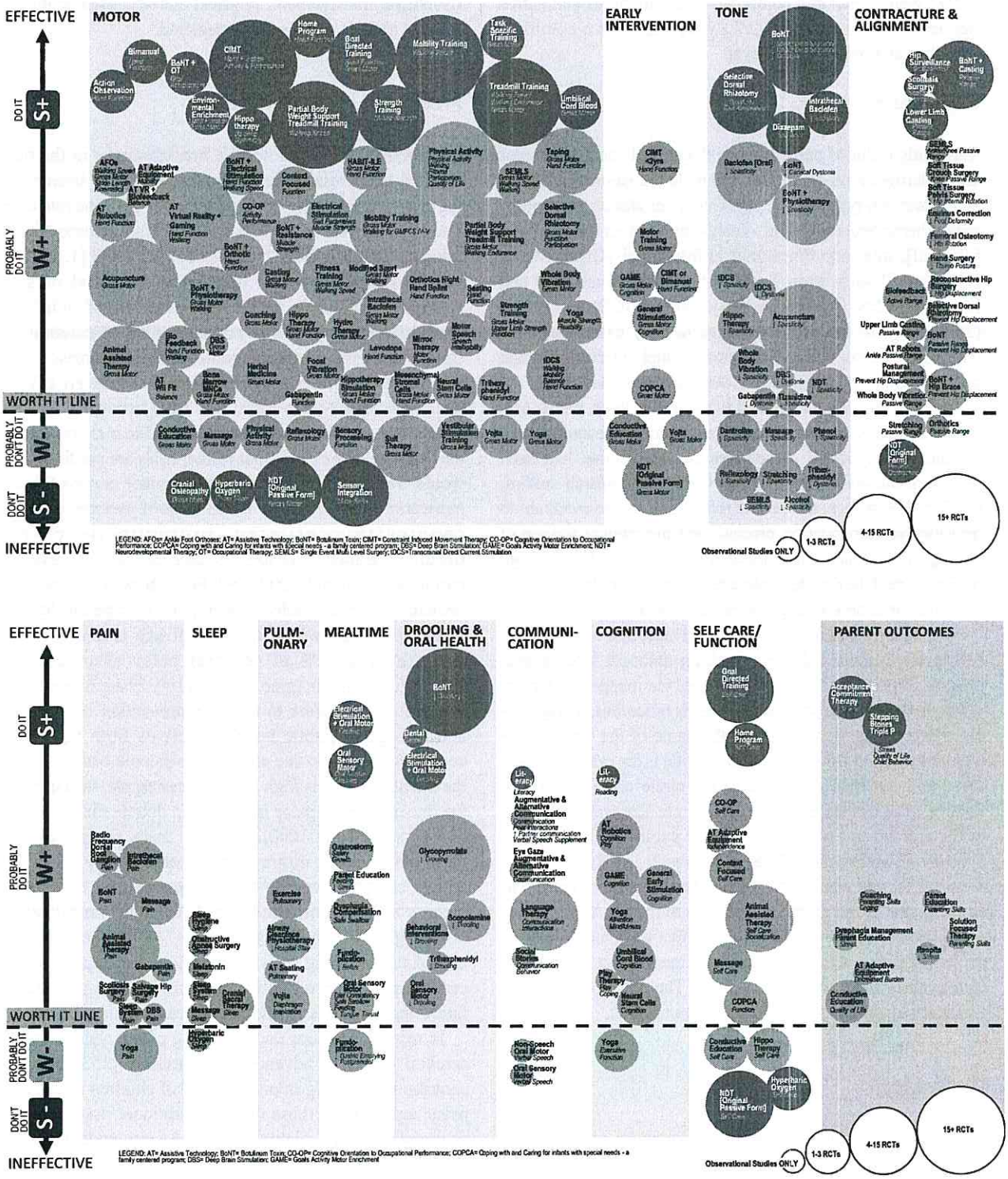

Fig. 2 Evidence Alert System. AFOs ankle-foot orthoses, AT assistive technology, BoNT botulinum toxin, CIMT constraint-induced movement therapy, CO-OP cognitive orientation to occupational performance, COPCA coping with and caring for infants with special needs—a family centered program, DBS deep brain stimulation, GAME goals activity motor enrichment, NDT neurodevelopmental therapy, OT occupational therapy, SEMLS single-event multi-level surgery, tDCS transcranial direct current stimulation

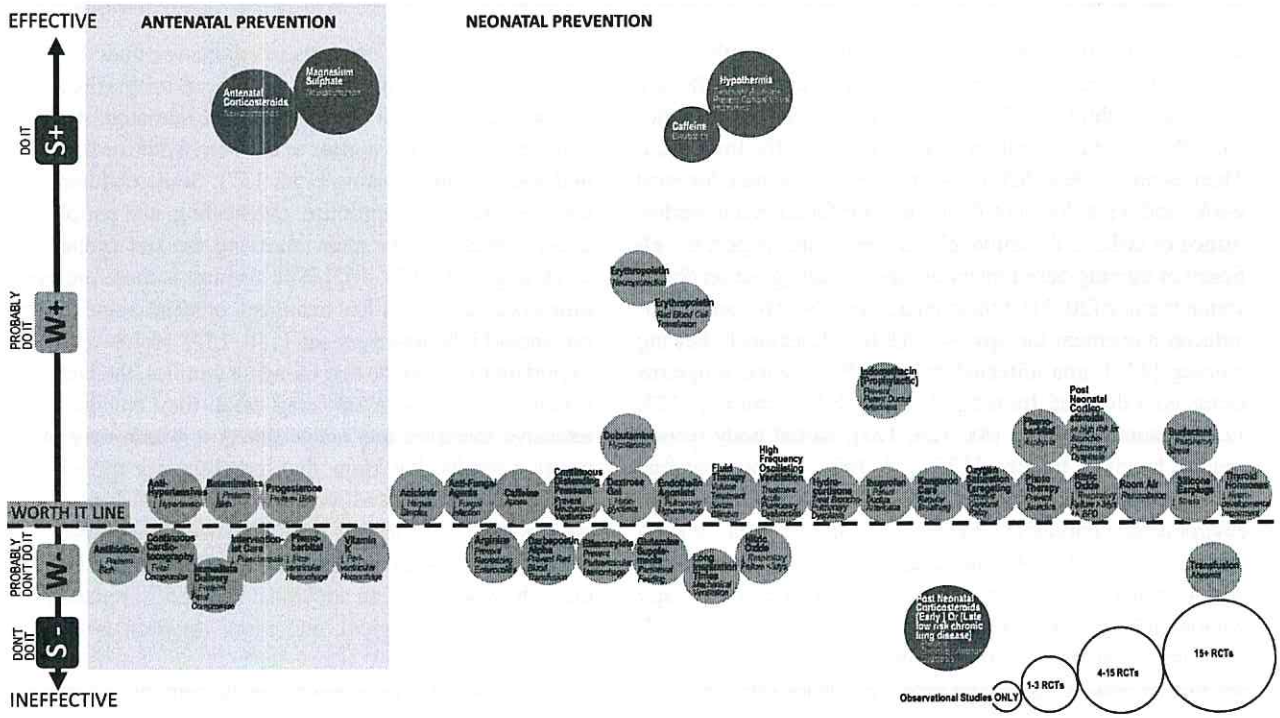

Fig. 2 continued

The field has also started to critically examine whether repair of a brain injury might be possible using regenerative medicine treatments, paving the way towards finding a cure. Our review found that erythropoietin has promising effects as a neuroregenerative treatment in the preterm population (yellow light, weak positive) and erythropoietin trials are underway in a population with hypoxic ischemic encephalopathy [11••]. In addition, there is now moderate-quality evidence that umbilical cord blood as a cell therapy, coupled with rehabilitation, is slightly more effective than rehabilitation alone for improving motor skills in children with cerebral palsy (green light) [221, 222]. The lack of legislation allowing access to autologous (patient's own) and/or matched allogeneic (donor) cord blood makes the feasibility of this treatment challenging.

Management of Cerebral Palsy

An intervention may target multiple desirable treatment outcomes, e.g., reduction of spasticity and improvement in function, and thus outcomes and levels of evidence could vary between outcomes. For most instances, the treatment outcome matched with the appropriate mechanism of action, e.g., pharmacological agent to reduce spasticity effectively reduced spasticity. There was often less convincing evidence (both in quality and volume) to support upstream effects for other treatment outcomes for other levels of the ICF, e.g., improvement in functional mobility. These are not surprising results; however, they provide an important reminder to clinicians to select interventions that address a child's specific goal based on the intervention's mechanism of action. Also, to be cognizant that applying more than one intervention simultaneously might be beneficial to achieve a goal where multiple goal-limiting factors are present. If the goal is to improve functional mobility: a pharmacological agent to reduce background spasticity (green light) [185] might make it easier to learn to move. Similarly, increasing lower limb muscle strength via strength training (green light) may improve related strength and endurance [151, 152], but principally targeted functional mobility training intervention will be required to establish an improvement in functional mobility (green light) [123, 127]. In all likelihood, the outcomes will be better if a combination of interventions are used. Some families believe that certain therapeutic approaches work for their child, but this was not possible to address within this review; however, we do not dismiss their views.

Motor Interventions

All children with cerebral palsy have, by definition, a motor impairment and difficulties with tasks involving motor performance [255]. In high-income countries, severity is lessening, and the rate of co-occurring epilepsy and intellectual disability is falling [2]. Three in four will now walk [2]. This decline in severity is encouraging. Children with cerebral palsy may be more likely than ever to be treatment responsive to motor

interventions, because smaller brain injuries result in improved baseline motor, sensory, and perceptual skills and learning capabilities. Thus, understanding current evidence for effective motor interventions is critically important. There is now a clear dichotomy in the evidence base for what works and what does not for improving function and performance of tasks. Substantive clinical trial data support the efficacy of training-based interventions, including action observation training [20, 21], bimanual training [54–56], constraint-induced movement therapy [46, 62–67], functional chewing training [137], goal-directed training [98], home programs using goal-directed training [112], mobility training [123, 127], treadmill training [65, 123, 127], partial body weight support treadmill training [123, 127, 169], and occupational therapy post botulinum toxin [190] (green lights). Moreover, environmental enrichment to promote task performance is effective (green light) [95] and adapting the environment and task to enable task performance via context-focused therapy (yellow light) [77] is a potent modulator of effective care. All these interventions have the following features in common: practice of real-life tasks and activities, using self-generated active movements, at a high intensity, where the practice directly targets the achievement of a goal set by the child (or a parent proxy if necessary). The mechanism of action is experience-dependent plasticity [256]. Motivation and attention are vital modulators of neuroplasticity, and successful task-specific practice is rewarding and enjoyable to children, producing spontaneously regular practice [256]. In stark contrast, bottom-up, generic, and/or passive motor interventions are less effective and sometimes clearly ineffective for improving function and movement for children with cerebral palsy. These include craniosacral therapy [239–241], hyperbaric oxygen [234, 235], neurodevelopmental therapy in the original passive format [108, 129–132], and sensory integration [3] (red lights). When viewed through the lens of neuroplasticity, these results are logical. A passive experience of a movement, provided via a hands-on therapeutic approach from a carer or therapist, does not involve any child-initiated problem solving or any child activation of their motor circuitry.

There are also several adjunctive interventions that when combined with task-specific motor training may augment the positive effects of training. These include electrical stimulation [65, 92–94], hydrotherapy [108, 110, 111], taping [159–164], transcranial direct current stimulation [101, 166–168], and virtual reality serious gaming [33–47] (yellow lights, weak positive). These interventions warrant more research as children reported finding gaming interventions rewarding and normalizing, and preferred electrical stimulation to wearing ankle-foot orthoses from a comfort perspective [93]. Also, taping is better tolerated than traditional orthotics with children often reporting discomfort and dissatisfaction with these interventions or disliking the cosmetic effect [73, 140]. Other benefits from these adjunctive interventions include cardiorespiratory fitness and social integration, and the importance of which cannot be underestimated. Adjunctive suit therapy does not appear to have any additive benefit over and above motor training [156, 157]. Some children experience respiratory compromise, overheating, and peripheral cyanosis which resolve after removing the suit (yellow light, weak negative) [156, 157]. Suit therapy is therefore not recommended as a front-line treatment, or stand-alone treatment, nor should it be unsupervised [156, 157]. However, it is very important to recognize that for some families, the process and routine of donning a suit may mean they engage in more intensive therapies and active practice, which may produce positive results. We know that intensive task-specific motor practice is effective and works in a variety of treatment modalities [98]. The theory behind transcranial direct current stimulation having an augmentative effect to motor training, through provision of an additional targeted stimulation of the motor cortex, is logical, and more research is warranted [166–168].

The available studies about complementary and alternative medicine interventions for childhood cerebral palsy aimed to improve motor skills. Trials suggested efficacy with acupuncture [227, 228] and animal-assisted therapy [102] (yellow lights, weak positive). In contrast, conductive education [231, 232], massage [238], reflexology [243], Vojta [244–246], and Yoga [248] were probably ineffective for improving motor skills (yellow lights, weak negative), and cranial sacral osteopathy [239–241] and hyperbaric oxygen [234] showed no between-group differences for motor skills in moderate-quality trials and serious side effects occurred (red lights). Proponents of conductive education would claim that because the approach is holistic, that it is not reasonable to analyze indicators in isolation; nevertheless, these are the motor outcome results from published clinical trials. It is therefore important to note, conductive education may have benefits for social skills and quality of life outcomes [231]. The manual therapies, including massage (green light) [237] and cranial sacral osteopathy [241] and reflexology [243] (yellow lights, weak positive), appeared to help reduce constipation. Massage also appeared to help reduce pain [3•] (yellow light, weak positive), whereas Yoga did not [248] (yellow light, weak negative). However, Yoga did appear to improve attention, muscle flexibility, and balance (yellow light, weak positive) [248].

Tone Management

Eighty-five percent of children with cerebral palsy have spasticity as their primary motor type and 7% have dyskinesia (including either dystonia or athetosis) as their primary motor type [2]. Many children have a mixed presentation involving both motor types [2]. Spasticity and dystonia cause

involuntary movements and postures that affect motor control and can be painful. Our review identified that the following pharmacological agents and neurosurgical procedures effectively reduce spasticity: botulinum toxin [185], intrathecal baclofen [175, 176], diazepam [3•], and selective dorsal rhizotomy [209] (green lights), plus dantrolene [3•] and tizanidine [3•] are probably effective (yellow light). Supplementary local injections of alcohol probably reduce spasticity [3] (yellow light, weak positive), and local injections of phenol also probably reduce spasticity very short-term, but side effects are common (yellow light, weak negative) [195]. Less research involves dystonia management, given the lower prevalence and under-recognition of this motor disorder. Probably effective pharmacological agents for reducing dystonia include local injections of botulinum toxin [3•], oral gabapentin [193], intrathecal baclofen via a pump [177] (yellow light, weak positive), and oral trihexyphenidyl, which may reduce dystonic and athetoid involuntary movements and improve participation, but side effects may outweigh the benefits for some children (yellow light, weak negative) [177, 196]. There is as much art as there is science to prescribing pharmacological agents, especially for children with cerebral palsy that have multiple medical comorbidities. For example, in a child with combined dystonia and epilepsy, may benefit from using one medication that addresses both symptoms such as gabapentin, instead of two medications targeting the symptoms individually. Additionally, botulinum toxin [187], intrathecal baclofen [179, 180], and gabapentin [179] appear to reduce pain (yellow light, weak positive), which may further support the clinical decision to trial these agents, despite this not being the primary mechanism of these agents, as the multiple benefits may make them an acceptable intervention to children and parents. Deep brain stimulation appeared promising for children with dystonia that caused pain and severely limited daily participation and more research is warranted [177, 198].

Against the backdrop of spasticity management, there is a now an intense research focus on improved understanding of pathology, histochemistry, and muscle architecture in cerebral palsy [257]. Children with cerebral palsy appear to have elevated proinflammatory cytokines and genes involved in the extracellular matrix of their skeletal muscles, combined with increased intramuscular collagen and reduced ribosomal production [258]. Newer understandings of these pathophysiological muscle changes have led some clinicians to call for a reconsideration of botulinum toxin treatment, which induces therapeutic weakness and potential muscle fibrosis [259]. We do not yet know whether the observed atrophy and insertion of replacement fat and connective tissue observed in muscles of children with cerebral palsy is the result of a direct or accelerated adverse event from botulinum toxin or whether these changes are the natural history of cerebral palsy. We anticipate that more research into muscle pathology will both alter treatment recommendations over time and, more importantly, lead to the discovery of new interventions.

Contracture Prevention and Management

Contracture is a common complication, particularly for children with spastic cerebral palsy. A longitudinal population-based study in Sweden has demonstrated that comprehensive multidisciplinary intervention at the right time can prevent contracture [260]. Contracture prevention and management should be thought of as a continuum, which will now be described. (a) In the early years, experts recommend high intensity self-generated active movement to prevent the onset of weakness, disuse and contracture [261]. While no clinical trial data is currently published supporting this idea, the hypothesis is currently being tested in clinical trials. (b) In Sweden, before contracture develops, the following interventions are used as part of comprehensive care: active movement, standing in standing shells (custom molded standing frames) for children GMFCS IV-V, and spasticity management using botulinum toxin where indicated. (c) Our review has shown that once a contracture has begun to develop, serial casting can be applied to effectively reduce or eliminate early/moderate contractures in the short term (green light). Notably, the skill of the practitioner in correctly aligning the joint and applying the cast is known to affect the result. For example, it is possible to perceive that increased range of motion has been achieved from casting, when in fact a further loss of biomechanical alignment of the midfoot (known as a midfoot break) has been induced, with no improvements in the hind foot. Casting effects can be enhanced by applying casts four weeks after botulinum toxin injections when the spasticity has been reduced (green light). Data indicates that children tolerate casting better when it is applied four weeks post toxin injection rather than immediately. The secondary weakness and altered proprioception induced from casts (with or without botulinum toxin) must be considered. Emergent evidence suggests that changing the casts at 3-day intervals rather than weekly intervals can shorten the total duration of the casting series and thus lower the amount of weakness induced. After casting, active strength training [60] (green light) and goal-directed training [98] (green light) are recommended to make functional use of the new range gained. (d) Once a contracture is severe (e.g., greater than 20°) and longstanding, casting will no longer be sufficient in isolation, and orthopedic surgery requires consideration. Some children and some muscles do not ever respond well to casting and proximal muscles cannot ever be cast; thus, surgical decision-making will be different in these scenarios. Moreover, casting requires regular appointments at specialist centers which may not be feasible for families in rural and remote locations. Orthopedic surgery may also be considered well before a contracture is severe, in order to maintain alignment, muscle length, and optimize biomechanics. The treating surgeon will consider the clinical examination, functional level,

and child's age, optimizing the timing of the surgery and minimizing the number of repeat procedures they will need over a childhood. Biomechanically, all joints in the lower limb work together in gait, meaning surgical lengthening of muscles at one joint impacts available range and control at other joints. Therefore, single-event multi-level surgery is a powerful intervention to simultaneously address the biomechanics of gait and minimize repeat surgeries (yellow light) [216, 217]. Our review has shown that traditional interventions for contracture management, including neurodevelopmental therapy [3•] (red light) and passive stretching in isolation [155] (yellow light), appear ineffective and the panel assigned negative recommendations since effective substitutes exist. In contrast, we found emergent low-quality evidence suggesting ankle robotics [32], biofeedback [30], botulinum toxin plus electrical stimulation [190], and whole-body vibration [97] may help manage contracture, by eliciting antagonist muscle activity that counterbalance involuntary agonist muscle contractions (yellow light), though more research is needed in this area.

Hip Surveillance

One in three children in high-income countries experience progressive hip displacement as a complication of their cerebral palsy, except in the Nordic countries where rates are substantially lower [260, 262]. There is moderate-quality evidence and a strong recommendation to use comprehensive hip surveillance practices to facilitate early detection and management of hip displacement (green light). It may initially seem contradictory that hip surveillance is allocated a green light while the orthopedic and physiotherapy interventions designed to prevent hip displacement are coded yellow. This paper reports purely on the best available evidence, coded using the GRADE framework. We observe that interventions in isolation (including botulinum toxin, intrathecal baclofen, selective dorsal rhizotomy, obturator nerve blocks, positioning, and bracing) have small effect sizes for preventing hip migration [145, 147]. In contrast, important clues arise from longitudinal population-based studies in Sweden, which have shown that comprehensive multidisciplinary intervention (including botulinum toxin, weight-bearing, motor training, and orthopedic surgery) at the right time and the right dose can prevent hip dislocation [260]. We, therefore, conclude that management of the hip surveillance must be early, timely, and comprehensive, and clinical practice guidelines exist to inform and guide best management (https://www.ausacpdm.org.au/resources/australian-hip-surveillance-guidelines/).

Physical Activity

Physical activity is essential for improving health but designing and implementing moderate to vigorous exercise programs for children with severe physical disabilities, who have limited movement and move slowly, is complex [263]. Recommendations to concurrently increase moderate to vigorous physical activity and replace sedentary behavior with light physical activity have been proposed to improve health [263]. New trials indicate that physical activity interventions (including exercise, activity training, strength training, and behavioral change strategies) probably improve fitness [144], physical activity [142–144], ambulation [144], mobility [144], participation, and quality of life [142] (yellow lights, weak positive). However, they do not appear to improve gross motor skills (yellow light, weak negative) [96, 144].

Participation

We observed a shift in interventions that affected a child's participation within their community. Most importantly, we noticed that interventions had been developed since 2013, which were specifically designed to target participation, and address barriers that prohibit participation and their effects were being studied in trials underway [264]. In other words, the targeted participation intervention was acting directly at the participation level of the international classification of function. There was a shift away from anticipating non-participation-based interventions might confer participation gains upstream.

Dysphagia Management

Half of all children with cerebral palsy have dysphagia and the prevalence is even higher in the infant population [265]. One in 15 will require non-oral tube feeding [262]. Dysphagia management is extremely important because aspiration resulting in respiratory complication is a leading cause of death in individuals with cerebral palsy (45%) [266]. Experts have called for greater attention to respiratory health given the lack of preventative strategies and low levels of evidence for management strategies (airway clearance techniques, oral sensorimotor therapy, compensatory strategies such as positioning and thickening fluids, sialorrhea management, upper airway interventions, antibiotics, gastro-intestinal interventions, and spinal surgery) (yellow lights) [22]. We identified two newer dysphagia management approaches in the evidence base which positively address feeding skills and potentially lower the risk of aspiration: (a) Electrical stimulation plus oral sensorimotor therapy conferred better lip closure during swallowing, the ability to swallow food without excess loss, the ability to sip liquid, the ability to swallow liquid without excess loss, and the ability to swallow without cough than sham electrical stimulation plus oral sensorimotor therapy (green light) [138]. No adverse effects were reported in the studies included in this review; however, immediate and longitudinal safety concerns have not yet been well documented. As such, given that this intervention approach yields only

modest benefits above and beyond oral sensorimotor therapy alone, a considered approach is warranted within a pediatric population. (b) A new motor learning–based oral sensorimotor intervention called functional chewing training (FuCT) appeared to improve chewing and reduce tongue thrust and sialorrhea better than traditional oral sensorimotor treatment alone [137] (yellow light), suggesting the direct training component was important. The FuCT findings are consistent with current thinking about motor learning. However, it must be noted that FuCT uses a combination of direct interventions, utilizing food or fluid; indirect interventions, utilizing nonnutritive tools to develop chewing skills; and sensory stimulation such as passive massage. Translation of this principle within the dysphagia management evidence base is becoming more prominent. Further research that compares direct, indirect, sensory, and compensatory interventions would be helpful in determining which approach results in greater skill development.

Early Interventions

Rates of cerebral palsy following prematurity, encephalopathy, and neonatal surgery are well understood. It is now possible to accurately detect and diagnose cerebral palsy as early as three months of age (corrected), enabling much earlier intervention [267]. Previously only 61–64% of infants with cerebral palsy were referred for intervention before 12 months of age due to late diagnosis [267, 268]. This directly affected the volume and methodological quality of early intervention clinical trials conducted and published for infants with cerebral palsy. An important turning point in the field was the publication of a systematic review identifying that child-active motor learning early interventions appeared to confer improved movement and cognition (yellow light, weak positive), whereas passive approaches such as neurodevelopmental therapy produce no better movement skills than untreated controls (yellow light, weak negative) [79, 80]. Recently, there has been a burst of small pilot trials conducted, testing the feasibility, acceptability, and preliminary efficacy of a range of novel motor learning training-based interventions adapted to be infant-friendly. These novel interventions (baby-CIMT [85], baby-bimanual [86], GAME [83, 84], small steps [82]) have reported positive gains in movement skills (yellow light, weak positive) confirming the findings of Morgan et al.'s (2016) systematic review [79]. More extensive replication trials are underway in these early interventions using rigorous designs with adequate statistical power, meaning more will be known in the next few years about the efficacy of motor learning training-based early intervention for cerebral palsy.

In contrast, the feasibility and preliminary efficacy trials of a novel parent coaching-based approach (COPCA) disappointingly did not confer any gains over and above passive neurodevelopmental therapy within traditional physiotherapy (yellow light, weak positive) [87–90]. Likewise, conductive education [91] and Vojta therapy [79, 80] for infants with cerebral palsy also appear ineffective for improving movement skills (yellow light, weak negative). Neither of these approaches are based upon motor learning theory, and thus seem to further confirm the findings of the pivotal systematic review which identified motor learning to be key [79]. Trials into early interventions targeting other developmental domains which can be affected in cerebral palsy including cognition, feeding, and communication will emerge in the near future.

Cognitive Interventions

Almost half of all children with cerebral palsy have co-occurring intellectual disability (46%) of varying severities, but notably, the prevalence of this comorbidity declining [1, 2, 262]. Co-occurring intellectual disability, coupled with severe physical disability, is known to elevate the risk for premature death during childhood [266]. With the shift in thinking about early motor interventions, the field has also started to explore whether the cognition of children with cerebral palsy can be modified and optimized. Early interactive reading and participation in early education settings, such as preschool, is known to improve intelligence in the typically developing and social risk populations, especially if these interventions include specific language development components [269]. In the cerebral palsy field, there is a shift towards actively recommending and testing these cognitive interventions with children with cerebral palsy. Our review found newer evidence of literacy interventions tailored for children with cerebral palsy using communication devices were effective (green light) [117, 118]. Infants that received GAME intervention (a combination of motor training, environmental enrichment, and coaching) had better cognition at 1 year of age than age-matched peers on a norm-referenced test (yellow light, weak positive) [83, 84]. More research on enriching the cognitive skills of infants with cerebral palsy is warranted.

Another innovation has been to test the feasibility, acceptability, and preliminary efficacy of a cognitive-based intervention known as cognitive orientation to occupational performance (CO-OP) [270]. CO-OP was originally designed for the developmental coordination disorder population where dyspraxia is the most important clinical sign [270], but now has promising evidence of efficacy for cerebral palsy, especially the dystonic type where treatment options are lacking [73–76]. In CO-OP, children set their own goals and are guided to discover and individualize strategies for successfully carrying out their goals, via a global problem-solving strategy "goal-plan-do-check" [270]. Once the child has self-identified a successful strategy, they practice the real-life task at high intensity, similar to other motor learning approaches [98]. Four studies have now been conducted in the cerebral palsy population suggesting

CO-OP improves function at a low dose and low cost with large effect sizes (yellow light, weak positive) [73–76]. The conduct of a definitive trial is warranted.

Parent Interventions

Parenting a child with cerebral palsy is known to be isolating and stressful. Supporting parents is essential both to optimize the child's development and to protect a parent's mental health. We observed that two interventions for parents of children with cerebral palsy, stepping stones triple P and acceptance and commitment therapy (ACT), now have empirical evidence of effectiveness (green lights) [19]. Stepping stones focuses on enhancing parenting skills and ACT focuses on increasing parental flexibility and enhancing a parent's ability to use their parenting skills in a stressful context [19]. The early and intentional support of parents offers important possibilities for improving children's outcomes.

A Guide to Interpretation

This paper is not the personal opinions of the authors; instead, it is a summary of the best available published evidence in 2019. This paper does not, therefore, invalidate observations of a child's response to interventions, even if they differ to average treatment responses measured in trials. Furthermore, it does not seek to criticize therapy choices of families or critique health care providers. Where evidence is not available, more well-designed trials are necessary. As cerebral palsy is a heterogeneous condition, the interpretation of the results from randomized controlled trials is complex.

Randomized controlled trials by their nature summarize the average response to an experimental treatment compared with that of a controlled comparison. In any given trial or real-world clinical scenario, an individual with cerebral palsy may respond better, or worse, than the average trial data. Heterogeneity is why many of the included trials have wide confidence intervals, indicating varied responses. We observed that often the trials with most robust treatment effects focused on homogeneous sub-groups of cerebral palsy (e.g., hemiplegia). In the future, alternative methodologies such as the *n* of 1 trial may accommodate the issue of heterogeneity.

To use the findings of this paper within clinical practice, we recommend the following: First, ask the child and family to define intervention goals. Second, match their goals to the outcome indicator headings and look up the corresponding intervention options with the associated levels of evidence. Third, select the intervention with the highest level of evidence and explain to families that on average, X intervention is most likely to help someone achieve their goals, and offer it. Monitor the individual effects of the intervention for the goal. Fourth, if the intervention is ineffective or unavailable, or the family declines (e.g., tried previously or side effects occurred), select the second most effective intervention and explain that on average, Y intervention is next most likely to help reach goals. Continue with this transparent conversation, compassionately acknowledging the disappointment if the child does not respond. Collectively problem solve a plan that matches the child's capabilities and optimizes inclusion.

Study Limitations

Our study has several limitations. First, a systematic review of systematic reviews is a study limitation in its own right because the methodology does not create any new knowledge that was not already published. In addition, the methodology of systematic reviews established by Cochrane favors the inclusion of randomized controlled trials, which may mean important observational studies are excluded or under-emphasized. Second, any summary lacks key details. Our helicopter view synthesis means that specific details about intervention fidelity, key ingredients, and best responders or non-responders are not reported or described in depth. We therefore advise clinicians and researchers to read additional literature to obtain this information, especially when adopting new interventions not previously used. Third, systematic reviews, despite being the highest level of evidence, are not without bias. Even though our review aimed to be unbiased, it included inherent biases. Publication bias may be at work within the included data we appraised, since trials with no between-group differences are less likely to be published in the first place, positively weighting the evidence base towards interventions that work. In addition, systematic reviews can be of varying methodological quality. Review authors may elect to include and review lower level evidence within their reviews to provide a more comprehensive picture of the evidence, but in doing so, provide a summary of highly biased data. We then have further summarized potentially biased data. The review authors may also have excluded relevant data, based on their inclusion criteria and the question they were seeking to answer. Fourth, in some of the included systematic reviews, we identified statistical errors, which we reinterpreted or reanalyzed where possible. For example, an accidental reversal of forest plots meaning the analysis was the opposite of the way the authors reported it. Another example was a misinterpretation of meta-analyses, where the confidence intervals around the standardized mean difference crossed the line of no effect, but the authors had made their interpretations based on the standardized mean difference alone and erroneously

interpreted the intervention as effective. Fifth, despite our thorough search strategy, there is no guarantee that we retrieved and included all relevant systematic reviews, or important data published after the included reviews that might have changed our confidence in the estimate of the effects. Sixth, as we excluded articles not published in English and adhered to strict inclusion criteria regarding % of participants identified as having cerebral palsy, we may have overlooked important data and/or excluded recent reviews exploring relevant, non-CP-specific interventions (for example *Augmentative and Alternative Communication*) due to participant numbers not reaching the required threshold. Some of the studies included in the reviews have reported on cerebral palsy but that may not be the primary outcomes of those studies.

Conclusion

Our paper systematically describes the best available evidence for cerebral palsy interventions in 2019, and highlights areas for more research. We found compelling evidence from systematic reviews to suggest the following: Green light prevention strategies: antenatal corticosteroids, magnesium sulfate, caffeine, and hypothermia. Green light allied health interventions: acceptance and commitment therapy, action observations, casting, constraint-induced movement therapy, environmental enrichment, fitness training, goal-directed training, hippotherapy, home programs, literacy interventions, mobility training, oral sensorimotor, oral sensorimotor plus electrical stimulation, pressure care, stepping stones triple P, strength training, task-specific training, treadmill training, partial body weight support treadmill training, and weight-bearing. Green light medical, surgical, pharmacological, and regenerative therapy interventions: anti-convulsants, intrathecal baclofen, bisphosphonates, botulinum toxin, botulinum toxin plus occupational therapy, botulinum toxin plus casting, diazepam, dental care, selective dorsal rhizotomy, scoliosis correction, hip surveillance, and umbilical cord blood cell therapy. In the last six years, many additional interventions have been researched, and the following interventions have been upgraded from emergent (yellow) to effective (green): Botulinum toxin plus adjunctive casting for increasing range of motion; goal-directed training for improving gross motor skills; hippotherapy for increasing symmetry; stepping stones triple P for improving child behavior; and strength training for improving muscle strength. There is a lack of robust clinical efficacy evidence for a large proportion of the interventions in use within standard care for people with cerebral palsy, and more research would increase our confidence in the estimate of effect. Thus, we have highlighted the need for more research using rigorous methodologies to advance the evidence base about interventions for cerebral palsy, to better inform decision-making by families and clinicians.

Compliance with Ethical Standards

Conflict of Interest Dr. Novak and coauthors have nothing to disclose.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors

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- • Of importance
- •• Of major importance

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13_CONCORSO PUBBLICO, PER TITOLI ED ESAMI, PER LA COPERTURA A TEMPO DETERMINATO, DELLA DURATA DI CINQUE ANNI PER N. 1 POSTO DI COLLABORATORE PROFESSIONALE DI RICERCA SANITARIA - CAT. D, DA ASSEGNARE ALLA UOC NEUROLOGIA DELLO SVILUPPO

PROVA 2

1. QUALI SONO I SEGNI CLINICI CHE CARATTERIZZANO IL BAMBINO CON SMA1, SMA2, SMA 3?

   IN UN BAMBINO DI 10 MESI CON DIAGNOSI DI SMA1:

   - QUALI ASPETTI VANNO VALUTATI E CON QUALI STRUMENTI?

   - QUALI SONO GLI OBIETTIVI GENERALI DEL TRATTAMENTO RIABILITATIVO?

2. LE RIGHE DI EXCEL SONO IDENTIFICATE TRAMITE:
   a. CIFRE ARABE
   b. NUMERI ROMANI
   c. LETTERE MINUSCOLE

3. LEGGA E TRADUCA IL TESTO ALLEGATO TRATTO DALLA LETTERATURA SCIENTIFICA

12/11/2021 PROVA NON ESTRATTA

BMJ Open

Protocol for a multisite randomised trial of Hand–Arm Bimanual Intensive Training Including Lower Extremity training for children with bilateral cerebral palsy: HABIT-ILE Australia

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ABSTRACT

Introduction Children with bilateral cerebral palsy often experience difficulties with posture, gross motor function and manual ability, impacting independence in daily life activities, participation and quality of life (QOL). Hand–Arm Bimanual Intensive Training Including Lower Extremity (HABIT-ILE) is a novel intensive motor intervention integrating upper and lower extremity training. This study aimed to compare HABIT-ILE to usual care in a large randomised controlled trial (RCT) in terms of gross motor function, manual ability, goal attainment, walking endurance, mobility, self-care and QOL. A within-trial cost–utility analysis will be conducted to synthesise costs and benefits of HABIT-ILE compared with usual care.

Methods and analysis 126 children with bilateral cerebral palsy aged 6–16 years will be recruited across three sites in Australia. Children will be stratified by site and Gross Motor Function Classification System and randomised using concealed allocation to either receiving HABIT-ILE immediately or being waitlisted for 26 weeks. HABIT-ILE will be delivered in groups of 8–12 children, for 6.5 hours per day for 10 days (total 65 hours, 2 weeks). Outcomes will be assessed at baseline, immediately following intervention, and then retention of effects will be tested at 26 weeks. Primary outcomes will be the Gross Motor Function Measure and ABILHAND-Kids. Secondary outcomes will be brain structural integrity, walking endurance, bimanual hand performance, self-care, mobility, performance and satisfaction with individualised goals, and QOL. Analyses will follow standard principles for RCTs using two-group comparisons on all participants on an intention-to-treat basis. Comparisons between groups for primary and secondary outcomes will be conducted using regression models.

Ethics and dissemination Ethics approval has been granted by the Medical Research Ethics Committee of Children's Health Queensland Hospital and the Health Service Human Research Ethics Committee (HREC/17/QRCH/282) of The University of Queensland (2018000017/HREC/17/QRCH/2820), and The Cerebral Palsy Alliance Ethics Committee (2018_04_01/HREC/17/QRCH/282).

Trial registration number ACTRN12618000164291.

Strengths and limitations of this study

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

INTRODUCTION

Cerebral palsy (CP) is the most common physical disability in childhood[1] with an estimated prevalence of 1.4 in 1000 live births.[2] Six hundred children are newly diagnosed with CP each year, with greater than 35 000 people living with CP in Australia.[3] Over 61% of children with CP have 'bilateral' motor involvement, impairing movement on both sides of the body.[1] For some of these children, all four limbs and trunk are affected, making both walking and effective upper limb use challenging. These limitations significantly impact their independence and participation in home, school, work and community life.[4] People with CP have poorer health outcomes compared

with age-matched peers.[5] Increased severity of physical disability is associated with reduced general health, greater pain and discomfort,[5] reduced independence in daily life skills[6] and poorer vocational outcomes.[7] Interventions that reduce the impact of the physical disability and promote independence in daily life skills, inclusion and community participation are essential.

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

Since children with bilateral CP often have both upper and lower limbs involved, Hand–Arm Bimanual Intensive Training Including Lower Extremity (HABIT-ILE) was invented to treat both the upper and lower limbs concurrently. In children with unilateral CP, a randomised control trial (RCT) demonstrated the efficacy of HABIT-ILE for both the upper and lower extremities.[12] Results obtained from concurrent upper and lower extremity training were similar to those obtained by children who underwent upper extremity training alone.[13] These findings led researchers to test whether HABIT-ILE intervention might be helpful for children with bilateral CP.[14] A recent systematic review of interventions to improve upper limb function in children with bilateral CP, however, has found a large variety of different interventions addressing upper limb function, but most studies have weak to moderate methodological quality.[15] The strongest evidence was from a small quasi-RCT of HABIT-ILE, and the authors highlighted the need for further high-quality trials.[14] Compared with a waitlist control group, children with bilateral CP who underwent 84 hours of HABIT-ILE achieved significantly greater gains in manual ability (ABILHAND-Kids n^2=0.32, p<0.001), self-care on the Paediatric Evaluation of Disability Inventory (n^2=0.26, p=0.001), gross motor function on the Gross Motor Function Measure 66-item (GMFM-66: n^2=0.33, p<0.001), walking distance on the 6 min Walk Test (6MWT: n^2=0.17, p<0.03) and balance on the Paediatric Balance Scale (n^2=0.28, p<0.002). These promising results indicate that a larger RCT is warranted to confirm the efficacy of HABIT-ILE on manual ability and gross motor function for children with bilateral CP. This multisite RCT, HABIT-ILE Australia, will compare this intensive motor training approach to usual care in school-aged children with bilateral CP at a lower dose than the original study (65 hours vs 90 hours). This lower dose was selected based on potential acceptability and feasibility within the Australian context.

AIMS AND HYPOTHESES

Broad aim

This multisite RCT will be conducted in three Australian states (Queensland (QLD), New South Wales (NSW) and Western Australia (WA)) with 126 school-aged children with bilateral CP. This RCT with a pragmatic, single-blind design will determine if HABIT-ILE is more effective than usual care to improve manual ability (ABILHAND-Kids) and gross motor function (GMFM-66) immediately postintervention and retention at 26 weeks. Secondary outcomes will test the differential effects of HABIT-ILE compared with usual care on neuroplastic changes in brain structural integrity, functional and structural connectivity, walking endurance (6MWT), self-care and mobility (Paediatric Evaluation of Disability Inventory–Computerised Assessment Test (PEDI-CAT)), bimanual performance (Both Hands Assessment: BoHA), performance of and satisfaction with individualised occupational performance goals (Canadian Occupational Performance Measure (COPM)), and quality of life (QOL) (Cerebral Palsy Quality of Life (CP QOL) Questionnaire: CP QOL-Child or CP QOL-Teen) immediately postintervention and retention at 26 weeks after the intervention.

Primary hypotheses

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

1. Manual ability on the ABILHAND-Kids by a difference of 1.6 logits or greater.
2. Gross motor function on the GMFM-66 by a difference of 5 points or greater.

Secondary hypotheses

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

1. Brain structural integrity measured using functional MRI (fMRI)-guided tractography.[16]
2. Walking endurance (6MWT).[17]

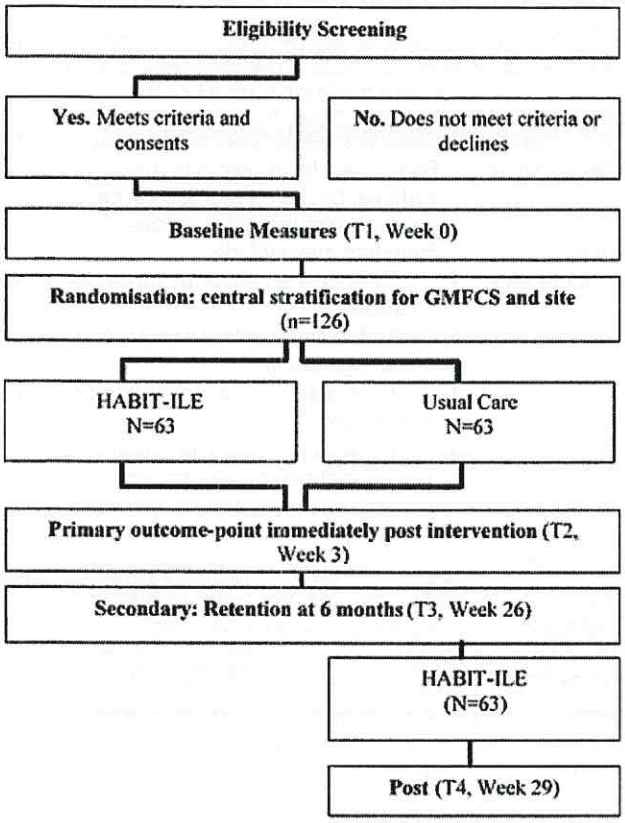

Figure 1 Participant flow diagram for HABIT-ILE Australia. GMFCS, Gross Motor Function Classification System; HABIT-ILE, Hand–Arm Bimanual Intensive Training Including Lower Extremity.

3. Bimanual hand performance (Both Hands Assessment (BoHA)).[18]
4. Self-care and mobility (PEDI-CAT).[19]
5. Performance and satisfaction scores on the COPM.[20]
6. QOL (CP QOL-Child or CP QOL-Teen, parent proxy and child report; and the Child Health Utility Index (CHU9) parent proxy).[21 22]
7. Cost effectiveness ($\Delta\$Cost/\Delta CP\ QOL$) of medical treatment received.

METHODS

Study design

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

Recruitment

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

Recruitment at each site will begin following ethical and governance approvals. Recruitment will draw on current databases within each organisation, referrals from clinical services. Based on population numbers available on the Australian Cerebral Palsy Register (1240 potentially eligible participants) and well-established state-wide clinical networks, recruitment of 126 participants is feasible across the three sites. It is expected that final data collection will occur in July 2021.

Inclusion criteria

To be eligible for inclusion, participants must be

1. Diagnosed with bilateral CP (diplegia/triplegia/quadriplegia),
2. Gross Motor Function Classification System (GMFCS) levels II (walks with limitations) to IV (limited self-mobility but able to do a standing transfer with the assistance of one person).
3. Aged 6–16 years.
4. Able to grasp light objects and lift most impaired arm ≥15 cm above a table surface.
5. Able to understand instructions and complete testing.

Exclusion criteria

1. Uncontrolled seizures.
2. Had orthopaedic and/or neurological surgery in the 6 months prior to or scheduled during study period (eligible for inclusion if at least 6 months postsurgery, and/or returned to presurgical gross motor and upper limb function following selective dorsal rhizotomy and no longer undergoing postoperative rehabilitation).
3. A visual impairment interfering with treatment/testing.
4. Inability to undertake standing transfers and/or walk a few steps (with a walker).
5. A significant cognitive and/or behavioural impairment limiting the ability to follow instructions determined through discussions with the primary caregiver and/or during a screening assessment.
6. Non-English speaking.

Randomisation

A biostatistician will create one central randomisation schedule using computer-based random numbers (in blocks of various sizes ranging from 10 to 20) to receive HABIT-ILE immediately or to waitlist usual care. Children will be stratified based on site (QLD, NSW and WA) and GMFCS (II vs III–IV). After consent and baseline measures are completed, children will be randomised with the use of a REDCap randomisation module set up by non-study personnel.

Blinding

At all time points, the GMFM-66 and BoHA will be rated from videos[23] by a certified rater masked to both group allocation and timing of assessments. Parents and assessing clinicians will be masked to group allocation for baseline

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

Item	Experimental HABIT-ILE	Control traditional usual care
Name	HABIT-ILE	Traditional eclectic usual care.
Why	Rationale: Intense, repetitive, active motor learning induces activity-dependent neuroplasticity. Essential elements: 1. Goal directed (goals defined by child/caregiver). 2. Motor training with concurrent challenge for upper and lower limbs and posture. 3. Shaping. 4. Active practice of goals. 5. High repetition and intensity.	Rationale: Usual care is highly variable, based on biomechanical and neurodevelopmental principles. Elements may include 1. Goals defined either by child/caregiver or therapist. 2. Stretching, splinting and casting. 3. Strengthening. 4. Functional training (eg, multimodal joint movements). 5. Therapist physically facilitates more typical (normal) movement patterns with children who are passive recipients. 6. May involve active goal practice.
Materials	Therapy bench, fit ball, balance board to intensely and repeatedly challenge posture; activities/toys/games for children to actively develop bimanual hand skills with continuous practice of part and whole tasks. Whole-task practice of individually identified functional goals with specific materials related to each goal.	Splints, casts, adaptive equipment to compensate for tasks child cannot perform.
Who	Therapy students (physiotherapy, occupational therapy and exercise science), volunteer physiotherapists and occupational therapists working directly with child with a ratio of 2:1 interventionists:child. Experienced physiotherapists and occupational therapists who have completed standardised training in HABIT-ILE will supervise and mentor interventionists.	Occupational therapist and/or physiotherapist to the child.
How	Clinic setting.	Clinic, hospital, home or school setting.
How much	6.5 hours/day for 10 weekdays over a 2-week period (total of 65 hours)	Weekly, monthly therapist provided±home programme. Highly variable.
Tailoring	Tailored to the child's individually defined functional goals. Daily review of progress with a view to continually and incrementally increase the challenge.	May be generic (eg, strength training, casting and splinting protocols), but highly variable.
How well	Daily video footage of participants at the day camp will be taken and reviewed by the supervising team and HABIT-ILE developer (YB) every second to third day to ensure delivery of intervention as per protocol.	Detailed survey of parents about intervention approaches used. Contamination is not anticipated as intensive therapy interventions are not frequently available for children with CP.

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

assessments. Analyses will be conducted using coded group allocation.

Study interventions

The HABIT-ILE and control interventions are summarised according to the Template for Intervention Description and Replication (TIDieR) Checklist[24] in table 1.

1. HABIT-ILE is a motor learning approach simultaneously addressing coordination of the upper and lower limbs.[12] Key elements of HABIT-ILE:

Dose: The total dose is 65 hours of HABIT-ILE. The 65 hours will be achieved through a 2-week intensive group-delivered day camp for 6.5 hours/day over 10 days conducted during the school holidays. Results from our previous research in intensive upper limb training in unilateral CP[25–27] and from our systematic review of all upper limb interventions[8] indicate that 60 hours is likely to be a sufficient dose to achieve significant changes in motor performance, and the 2-week camps are feasible for children and their families. The model of HABIT-ILE to be tested has been adapted to maximise future clinical translation to ensure acceptability and feasibility to children with bilateral CP and their families in Australia.

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

Content and tailoring: Intervention will be based on the child's motor abilities (determined at baseline), age, interests and self-identified functional goals. Tasks/activities are

made incrementally more challenging. Practice is structured, using part-task and whole-task practice with high repetition and ongoing feedback about performance.[12 28] A process of shaping with progressive approximations is undertaken over 10 days. For example, if a pincer grasp is required for the goal (eg, do buttons up on school shirt) and the child is not yet performing this grasp effectively, children will practice tasks that progress incrementally towards this grasp. This requires a clinical reasoning process whereby components/impairments leading to the breakdown of goal performance are identified (eg, strength, active range of motion, coordination, and motor planning or strategy) then targeted with deliberately selected, incrementally challenging games and activities.

Upper extremity: Tasks that will be performed include (1) incremented table top fine motor activities, (2) activities of daily living when sitting/standing/walking, and (3) gross motor play and physical activities.

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

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

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

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

Adverse events and safety

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

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

Major adverse events include

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

After reporting to the site chief investigator, local site processes will be followed as necessary.

Fidelity

Therapist attributes

It is required that HABIT-ILE therapists at each site possess the following attributes:

- Full registration with the Australian Health Practitioner Regulation Agency (physiotherapists and occupational therapists).
- Current basic first aid and cardiac pulmonary resuscitation certificate.

It is highly desirable that therapists possess the following attributes:

- Three or more years of experience working with children with CP and their families.
- Experience working within models or frameworks of motor learning.

Therapist training

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

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

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

Fidelity monitoring

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

Screening and descriptive measures

All participants will be classified using the

1. Manual Abilities Classification System (MACS): The MACS will classify the child's ability to hand objects in daily activities on a five-level ordinal scale.[29] The MACS has established construct validity and excellent inter-rater reliability (intraclass correlation coefficient (ICC) 0.97 between therapists). It is expected that children in the study will be functioning at MACS levels I–III.[29]
2. GMFCS Expanded and Revised: The GMFCS classifies the child's ability to carry out self-generated movements related to sitting and walking on a five-level ordinal scale.[30] The GMFCS has established construct validity and good inter-rater reliability between therapists.[31]
3. Communication Function Classification System (CFCS): The CFCS will be used to classify children's everyday performance of communicating using all methods (eg, speech, gestures, eye gaze, augmentative and alternative communication) on a five-level ordinal scale.[32] There is evidence of content validity, good test–retest reliability and good inter-rater reliability (0.66) between professionals.[32 33]

Demographic Questionnaire: A study-specific demographic questionnaire will collect information on the child's age, gender, comorbidities, type of schooling, socioeconomic status, family structure and support, family income, and current involvement in rehabilitation programme.

Primary outcomes

1. *ABILHAND-Kids* is a Rasch-built parent completed questionnaire measuring the manual ability of children with CP.[34] The ABILHAND-Kids has demonstrated content, construct and evaluative validity, high internal consistency (α=0.94), excellent test–retest reliability (r=0.91)[34] and is responsive in detecting change following intensive upper limb motor training interventions (smallest detectible difference=0.81–1.03 logits).[35 36] The ABILHANDS has the strongest evidence of validity and reliability to measure hand function in children with bilateral CP[37] and is responsive to change.[35]
2. The *GMFM-66* is a criterion referenced observation measure developed using Rasch modelling to measure gross motor function of children with CP.[38] The GMFM-66 has established construct validity, high test–retest reliability (ICC 0.99)[38] and is responsive to change (minimal clinically important difference=1.5).[38–40]

Secondary outcomes

1. *Brain structural integrity:* Brain MRI will be conducted using 3T scanners. The child will be familiarised with the MRI procedures before the scan. During the MRI, the child will watch an age-appropriate movie of his or her choice, except during the acquisition of the fMRI. Structural brain images will be acquired using high-resolution 3D T1-weighted magnetization-prepared rapid acquisition with gradient echo (MPRAGE) and high-resolution 3D T2-weighted fluid-attenuated inversion recovery (FLAIR). Diffusion MRI data will be acquired using a multishell approach with 20 directions at b=1000 s/mm^2, 60 directions at b=3000 s/mm^2 and 8 non-diffusion-weighted images (b=0 s/mm^2). The acquisition will be split in four blocks (of 22 directions) to allow more efficient rescanning of data affected by motion. Half of the blocks are reverse phase encoded to assist in the correction of residual distortions due to susceptibility inhomogeneities. fMRI data will be acquired using a block design, with a simple active hand and passive foot-tapping task. Two two-dimensional gradient recalled echo images (echo timeTE1/TE2, 4.92/7.38 ms) were used to acquire a field map for functional data, which assists when correcting for distortion due to susceptibility inhomogeneities. The total scan time will be <1 hour.

   Structural brain images will be used for lesion scoring using the Fiori scale, a semiquantitative scale for use in brain imaging of CP.[41] Structural brain images will also be used to assess alterations in cortical thickness in response to therapy. Diffusion data will allow both traditional analysis using the diffusion tensor model (fractional anisotropy and mean diffusivity), as well as state-of-the-art tractography and calculation of advanced imaging microstructural biomarkers thought to closely reflect the status of the underlying brain tissue. fMRI-guided tractography will be carried out as described previously.[42 43]
2. *Walking endurance:* The 6MWT is a clinical exercise test measuring walking endurance with excellent test–retest reliability (ICC 0.98) for children with CP.[17] The test requires participants to walk as far as possible in 6 min using a 10 m track with cones demarcating the turning points. Participants will be given verbal and visual instructions before testing. Participants will be instructed to walk as far as possible without running in 6 min. Participants will be given verbal encouragement and will be advised every 30 s of the distance covered (in laps) and the time remaining. Distance will be measured to the nearest 1 m mark.
3. *Bimanual hand performance:* The BoHA measures how children who have bilateral CP use their hands together in bimanual activities.[18] The measure was developed through adaptation of the Assisting Hand Assessment. Rasch measurement modelling showed strong evidence of internal construct validity, with two separate item difficulty hierarchies for children with (1) symmetric upper limb use and (2) asymmetric upper limb use.[17] The test uses a selection of toys to elicit bimanual hand behaviour and can be administered in a structured play session or using the board game version, depending on the age of the child. The BoHA takes 15 min to complete. The assessment is video-taped for later scoring by a rater blinded to group allocation and who has been certified in its use.
4. *Self-care and mobility:* PEDI-CAT: The PEDI-CAT is a standardised, norm-referenced assessment of indepen-

dence in self-care. The test is valid, reliable and responsive in this population.[19] The PEDI-CAT is completed by parents using an iPad or a computer application. The item bank of the PEDI-CAT was developed using Rasch measurement modelling on large samples of typically developing children and those with disabilities. Two domains, self-care and mobility, will be completed by caregivers.

5. *Performance and satisfaction with occupational performance goals:* The COPM[20] will be used to measure performance of and satisfaction with individually defined self-care, leisure or productivity goals. Test–retest reliability is high (ICC 0.76–0.89), and the COPM is responsive to change.[20] Children 8 years and older can self-report, and caregivers can complete the COPM for younger children or those with cognitive difficulties that would preclude them from completing it independently. Children and their caregivers will set up to three goals. Perceived performance of an individualised goal and satisfaction with performance are rated on a 1–10 scale with higher scores reflecting higher perceived performance and satisfaction.
6. *QOL:* The CP QOL-Child is a 52-item, condition-specific self-report measure of child QOL that is specifically developed for measuring QOL in children with CP.[22] The majority of items have the stem 'How do you feel about…' with a response scale of 9 points from 1=very unhappy to 9=very happy. The domains covered in the child self-report version include physical well-being, social well-being, emotional well-being, school and acceptance by others. It has good concurrent validity, internal consistency (Cronbach's alpha 0.80–0.90) and test–retest reliability for children 9 years of age and over. Significant discordance exists between child and parent proxy reports in many health-related QOL instruments, and both the child and parent proxy perspectives will be sought in the present study. The CP QOL will be completed by all children, unless they are under the age of 9 years or have an intellectual disability. An adult who is not participating in the study as the primary parent/caregiver will read the questionnaire alongside the child and clarify the meaning of the questions and response scale if necessary. For teenagers 13 years of age or older, the adolescent version will be completed (CP QOL-Teen) by teens and their caregiver.[21]
7. The *CHU9D* is a paediatric health-related QOL measure for use in economic evaluation. The measure consists of nine questions. Children can self-report from 7 years of age, and parents can proxy report for their child. In this study, the Child Health Utility 9D (CHU9D) will be completed by the child's primary caregiver.[44]

Data management

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

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

Management of withdrawals

Participants can withdraw at any time. Participants who choose to withdraw from the study will not be penalised in any way. If they wish to continue with therapy intervention for their child, they will be assisted to source another local therapy option that matches their preferences. Participants are informed of their right to withdraw at any time without consequences at the time of reading participant information forms and signing of consent forms. Participants can enrol and undergo HABIT-ILE irrespective of whether they consent to the neuroimaging and/or economic analysis aspects of the study. Participants who withdraw will not be replaced, as the a priori power calculation will account for a 10% dropout rate and 10% crossover rate.

Sample size estimation

A 1.6 logit change on the ABILHAND-Kids was achieved in a small RCT of HABIT-ILE.[14] A sample of 126 (63 in each arm) yields 80% power, with significance at a two-sided alpha level of 0.05 to show a difference of 1.6 ABILHAND-Kids logits, with an SD of change of 3 and buffering for 10% attrition. We will have >90% power to detect a difference of 5 points or greater on the GMFM (assuming SD=6) and alpha=0.05, buffering for 10% attrition). For neuroimaging outcomes, a 1% change in fractional anisotropy using fMRI-guided tractography and a 6% change in cortical thickness are considered realistic estimates for current therapies. Our recent work on power analysis for imaging measures of neuroplasticity in CP suggests that, assuming an 80% success rate of MRI, 39 subjects are required to detect a 1% change in FA using fMRI-guided tractography, the most sensitive available method.[45]

Statistical analysis

Analyses will follow standard principles for RCTs using two-group comparisons on all participants on an intention-to-treat basis. Primary comparison immediately postintervention (T2) and retention at (T3) based on

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

Health economics

A within-trial cost–utility analysis[46] will be conducted to synthesise the costs and benefits of the HABIT-ILE programme compared with usual care. Resource use (staff/student time, equipment and facility use, and consumables) associated with the programme will be collected alongside the RCT. Healthcare use will be collected using a resource use questionnaire previously used in CP child studies.[47] Health utilities will be derived from the CHU9D,[44] a generic child QOL measure designed specifically for economic evaluation, which has been validated in an Australian population.[48] Incremental cost effectiveness ratios will be estimated and, where appropriate, sensitivity analyses will be undertaken.

Ethics and dissemination

Full ethical approval has been granted by the Children's Health Queensland Hospital and Health Service Human Research Ethics Committee (HREC/17/QRCH/282), the Medical Research Ethics Committee of The University of Queensland (2018000017/HREC/17/QRCH/2820) and Cerebral Palsy Alliance (2018_04_01/HREC/17/QRCH/282). Participant information and consent forms will be provided to all participants and their caregivers prior to entering the study. Full written and informed consent will be obtained from all caregivers of children participating in the trial. The trial has been registered with the Australian and New Zealand Clinical Trial Registry. This protocol is reported according to the Standard Protocol Items: Recommendations for Intervention Trials statement[49] and the TIDieR Checklist.[24]

Findings will be disseminated via peer-reviewed publication of study results, newsletter feedback to consumers, and presentation at key national and international conferences. The authors will plan a knowledge translation pathway if the intervention proves effective in improving ability to make and keep friends.

Public/patient involvement statement

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

DISCUSSION

Over 60% of children with CP have bilateral motor impairment impacting independence in activities of daily living, participation and QOL. To date, there is limited evidence for effective interventions to improve motor and functional outcomes in children with bilateral CP. Building on a previous small study,[14] the HABIT-ILE Australia project is the first large-scale study to test the efficacy of this intensive motor training intervention on motor and neuroimaging outcomes in children with bilateral CP. One potential limitation of the study is that therapy students under the supervision of trained therapists will be primarily delivering the HABIT-ILE intervention. This will be accounted for by providing 1 day of standardised training for all interventionists, daily debriefing meetings at the end of each day and ongoing daily feedback from supervising therapists. In addition, fidelity checks with the HABIT-ILE developer (YB) will occur throughout the conduct of each HABIT-ILE camp. Second, the dose being tested (65 hours) was a pragmatic choice based on what is likely to be feasible and acceptable in the Australian context. This dose, however, is less than that in previous studies (90 hours). This study will additionally determine whether HABIT-ILE is translatable and implementable to a broad Australian setting.

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

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13_CONCORSO PUBBLICO, PER TITOLI ED ESAMI, PER LA COPERTURA A TEMPO DETERMINATO, DELLA DURATA DI CINQUE ANNI PER N. 1 POSTO DI COLLABORATORE PROFESSIONALE DI RICERCA SANITARIA - CAT. D, DA ASSEGNARE ALLA UOC NEUROLOGIA DELLO SVILUPPO

PROVA 3

1. QUALI SONO I SEGNI CLINICI CHE CARATTERIZZANO UN BAMBINO AFFETTO DA NEUROPATIA GENETICAMENTE DETERMINATA?

   CON QUALI SCALE TESTALI LO VALUTA?

   QUALI ATTIVITÀ ED ESERCIZI CONSIGLIA?

2. IN ACCESS COSA È UNA "QUERY"?
   a. UNO STRUMENTO IDONEO ALL'INTERROGAZIONE ED ALLA MANIPOLAZIONE DEI DATI
   b. UNA TABELLA DI VISUALIZZAZIONE DI ATTRIBUTI DI UN ELEMENTO GEOGRAFICO
   c. UNA TABELLA DI VISUALIZZAZIONE DI ATTRIBUTI DI UN ELEMENTO GRAFICO

1. LEGGA E TRADUCA IL TESTO ALLEGATO TRATTO DALLA LETTERATURA SCIENTIFICA

Sofia Olobardi 12/11/2021 PROVA ESTRATTA

[Intervention Review]

Constraint-induced movement therapy in children with unilateral cerebral palsy

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ABSTRACT

Background

Unilateral cerebral palsy (CP) is a condition that affects muscle control and function on one side of the body. Children with unilateral CP experience difficulties using their hands together secondary to disturbances that occur in the developing fetal or infant brain. Often, the more affected limb is disregarded. Constraint-induced movement therapy (CIMT) aims to increase use of the more affected upper limb and improve bimanual performance. CIMT is based on two principles: restraining the use of the less affected limb (for example, using a splint, mitt or sling) and intensive therapeutic practice of the more affected limb.

Objectives

To evaluate the effect of constraint-induced movement therapy (CIMT) in the treatment of the more affected upper limb in children with unilateral CP.

Search methods

In March 2018 we searched CENTRAL, MEDLINE, Embase, CINAHL, PEDro, OTseeker, five other databases and three trials registers. We also ran citation searches, checked reference lists, contacted experts, handsearched key journals and searched using Google Scholar.

Selection criteria

Randomised controlled trials (RCTs), cluster-RCTs or clinically controlled trials implemented with children with unilateral CP, aged between 0 and 19 years, where CIMT was compared with a different form of CIMT, or a low dose, high-dose or dose-matched alternative form of upper-limb intervention such as bimanual intervention. Primarily, outcomes were bimanual performance, unimanual capacity and manual ability. Secondary outcomes included measures of self-care, body function, participation and quality of life.

Data collection and analysis

Two review authors independently screened titles and abstracts to eliminate ineligible studies. Five review authors were paired to extract data and assess risk of bias in each included study. GRADE assessments were undertaken by two review authors.

Main results

We included 36 trials (1264 participants), published between 2004 and 2018. Sample sizes ranged from 11 to 105 (mean 35). Mean age was 5.96 years (standard deviation (SD) 1.82), range three months to 19.8 years; 53% male and 47% participants had left hemiplegia. Fifty-seven outcome measures were used across studies. Average length of CIMT programs was four weeks (range one to 10 weeks). Frequency of sessions ranged from twice weekly to seven days per week. Duration of intervention sessions ranged from 0.5 to eight hours per day. The mean total number of hours of CIMT provided was 137 hours (range 20 to 504 hours). The most common constraint devices were a mitt/glove or a sling (11 studies each).

We judged the risk of bias as moderate to high across the studies.

Key results: Primary outcomes at primary endpoint (immediately after intervention)

CIMT versus low-dose comparison (e.g. occupational therapy)

We found low-quality evidence that CIMT was more effective than a low-dose comparison for improving bimanual performance (mean difference (MD) 5.44 Assisting Hand Assessment (AHA) units, 95% confidence interval (CI) 2.37 to 8.51).

CIMT was more effective than a low-dose comparison for improving unimanual capacity (Quality of upper extremity skills test (QUEST) - Dissociated movement MD 5.95, 95% CI 2.02 to 9.87; Grasps; MD 7.57, 95% CI 2.10 to 13.05; Weight bearing MD 5.92, 95% CI 2.21 to 9.6; Protective extension MD 12.54, 95% CI 8.60 to 16.47). Three studies reported adverse events, including frustration, constraint refusal and reversible skin irritations from casting.

CIMT versus high-dose comparison (e.g. individualised occupational therapy, bimanual therapy)

When compared with a high-dose comparison, CIMT was not more effective for improving bimanual performance (MD −0.39 AHA Units, 95% CI −3.14 to 2.36). There was no evidence that CIMT was more effective than a high-dose comparison for improving unimanual capacity in a single study using QUEST (Dissociated movement MD 0.49, 95% CI −10.71 to 11.69; Grasp MD −0.20, 95% CI −11.84 to 11.44). Two studies reported that some children experienced frustration participating in CIMT.

CIMT versus dose-matched comparison (e.g. Hand Arm Bimanual Intensive Therapy, bimanual therapy, occupational therapy)

There was no evidence of differences in bimanual performance between groups receiving CIMT or a dose-matched comparison (MD 0.80 AHA units, 95% CI −0.78 to 2.38).

There was no evidence that CIMT was more effective than a dose-matched comparison for improving unimanual capacity (Box and Blocks Test MD 1.11, 95% CI −0.06 to 2.28; Melbourne Assessment MD 1.48, 95% CI −0.49 to 3.44; QUEST Dissociated movement MD 6.51, 95% CI −0.74 to 13.76; Grasp, MD 6.63, 95% CI −2.38 to 15.65; Weightbearing MD −2.31, 95% CI −8.02 to 3.40) except for the Protective extension domain (MD 6.86, 95% CI 0.14 to 13.58).

There was no evidence of differences in manual ability between groups receiving CIMT or a dose-matched comparison (ABILHAND-Kids MD 0.74, 95% CI 0.31 to 1.18). From 15 studies, two children did not tolerate CIMT and three experienced difficulty.

Authors' conclusions

The quality of evidence for all conclusions was low to very low. For children with unilateral CP, there was some evidence that CIMT resulted in improved bimanual performance and unimanual capacity when compared to a low-dose comparison, but not when compared to a high-dose or dose-matched comparison. Based on the evidence available, CIMT appears to be safe for children with CP.

PLAIN LANGUAGE SUMMARY

Constraint-induced movement therapy in the treatment of the upper limb in children with unilateral cerebral palsy

Review question

Does constraint-induced movement therapy (CIMT) improve arm and hand use in children with unilateral cerebral palsy (CP)?

What is the aim of this review?

To find out if CIMT helps children with unilateral (hemiplegic) CP to use their hands more effectively.

Key messages

CIMT may work better than another upper-limb therapy carried out at low intensity (low dose) for improving children's ability to use both hands together. CIMT appears no more effective than another upper-limb therapy carried out at a high dose or equal dose. CIMT appears to be safe. More well-designed research is needed for strong conclusions to be made.

What was studied in the review?

Children with unilateral CP have difficulty using two hands together. Most daily activities need co-ordinated use of two hands together, so clinicians use CIMT to help children with unilateral CP improve upper-limb ability. There is no one type of CIMT, although it always involves a constraint (e.g. mitt, sling, cast) on the less affected arm, accompanied by intensive therapy with the more affected arm.

What are the main results of the review?

Thirty-six studies were found. Children were involved in CIMT from 20 to 504 hours. CIMT studies were divided into three categories.

CIMT compared with a low-dose comparison group *(children had 0 to 25 hours of comparison therapy; and the amount of therapy was much lower than the amount of CIMT)*

CIMT may improve bimanual ability (that is, using both hands together; low-quality evidence) and unilateral capacity (that is, one-handed ability using the more affected hand; very low-quality evidence) more than low dose. Three studies reported that a small number of children experienced frustration or refused to wear the constraint, or had reversible skin irritations from casting.

CIMT compared with a high-dose comparison group *(children had more than 25 hours of bimanual therapy or another form of intensive therapy and the amount was less than CIMT)*

CIMT appeared no more effective than a high-dose comparison therapy on bimanual ability (low-quality evidence) or unimanual capacity (very low-quality evidence). Two studies reported that some children experienced frustration from participating in CIMT.

CIMT compared with a dose-matched comparison group *(children received the same amount of bimanual therapy as the CIMT group).*

CIMT appeared no more effective than dose-matched therapy on bimanual ability, unimanual capacity (low-quality evidence) or manual ability (very low-quality evidence). From 15 studies, two children did not tolerate CIMT and three had difficulty getting used to CIMT.

How up to date is this review?

The review includes studies published up to March 2018.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Constraint induced movement therapy (CIMT) compared to low-dose comparison for children with unilateral cerebral palsy

Constraint induced movement therapy compared to low-dose comparison for children with unilateral cerebral palsy

Patient or population: children with unilateral cerebral palsy
Setting: mixed (home, clinic, laboratory, pre-school)
Intervention: constraint induced movement therapy
Comparison: low-dose comparison

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with low-dose comparison	Risk with constraint induced movement therapy				
Bimanual performance Assessed with: Kids-Assisting Hand Assessment Scale from: 0 to 100 Follow-up: immediately postintervention	The mean bimanual performance in the control groups ranged from **0.57** to **1.0 AHA units**	The mean bimanual performance in the intervention groups was **5.44 AHA units higher** (2.37 higher to 8.51 higher)	-	39 (2 RCTs)[c]	⊕⊕⊖⊖ **Low**[a,b]	Higher score indicates improved bimanual performance.
Unimanual capacity Assessed with: Melbourne Assessment Scale from: 0 to 100 Follow-up: immediately postintervention	The mean unimanual capacity in the control group was **−0.05 points**	The mean unimanual capacity in the intervention group was **1.98 points higher** (1.55 lower to 5.51 higher)	-	23 (1 RCT)	⊕⊖⊖⊖ **Very low**[a,b,d]	Higher score indicates improved unimanual capacity.
Unimanual capacity Assessed with: Quality of Upper Extremity Skills Test - Grasps Scale from: 0 to 100 Follow-up: immediately postintervention	The mean unimanual capacity in the control groups ranged from **0.9 to 2.5 points**	The mean unimanual capacity in the intervention groups was **7.57 points higher** (2.10 higher to 13.05 higher)	-	103 (2 RCTs)	⊕⊖⊖⊖ **Very low**[a,b,c,e]	Higher score indicates improved unimanual capacity.
Manual ability - not measured	-	-	-	-	-	No studies measured manual ability.

Self-care - not measured	See comment	See comment	-	-	See comment	No studies measured self-care.
Individualised measures of performance - not measured	See comment	See comment	-	-	See comment	No studies measured individualised performance.
Adverse events	The presence or absence of adverse events were not mentioned in 8/16 studies. 3 studies reported 4 children were unable to tolerate constraint induced movement therapy		-	454 (16 RCTs)	-	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **MD**: Mean difference; **RCT:** randomised controlled trial.

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[a]Downgraded one level due to risk of bias (all studies are at high risk of bias because it is not possible to blind personnel or participants to group allocation).
[b]Downgraded one level due to small sample size (number of participants < 400).
[c]Downgraded one level due to inconsistency (heterogeneity statistically significant: $P < 0.10$, $I^2 > 40\%$).
[d]Downgraded one level because results are from a single study.
[e]Trial by Choudhary 2013 was registered in Clinical Trials Registry of India. Register stated one of the outcomes was: "To assess parent's perception of improvement in upper extremity function after four weeks of therapy and eight week follow-up, using parent questionnaire." No parent perception data were reported. We did not downgrade the body of evidence for unimanual capacity based on this finding.

Summary of findings 2. Constraint induced movement therapy (CIMT) compared to high-dose comparison for children with unilateral cerebral palsy

Constraint induced movement therapy compared to high-dose comparison for children with unilateral cerebral palsy

Patient or population: children with unilateral cerebral palsy
Setting: mixed (home, clinic, camp)
Intervention: constraint induced movement therapy
Comparison: high-dose comparison

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with high-dose comparison	Risk with constraint induced movement therapy				
Bimanual performance Assessed with: Assisting Hand Assessment-Kids Scale from: 0 to 100 Follow-up: immediately postintervention	The mean bimanual performance in the control groups ranged from**0.8 to 7 AHA units**	The mean bimanual performance in the intervention groups was **0.39 AHA units** lower (3.14 lower to 2.36 higher)	-	126 (3 RCTs)	⊕⊕⊖⊖ **Low**[a,b,c]	Higher score indicates improved bimanual performance.
Unimanual capacity Assessed with: Melbourne Assessement Scale from: 0 to 100 Follow-up: immediately postintervention	The mean unimanual capacity in the control group was **1.2 points**	The mean unimanual capacity in the intervention group was **2 points lower** (5.36 lower to 1.36 higher)	-	43 (1 RCT)	⊕⊖⊖⊖ **Very low**[a,b,d]	Higher score indicates improved unimanual capacity.
Unimanual capacity Assessed with: Quality of Upper Extremity Skills Test - Grasp Scale from: 0 to 100 Follow-up: immediately postintervention	The mean unimanual capacity in the control group was **3.31 points**	The mean unimanual capacity in the intervention group was **0.2 points lower** (11.84 lower to 11.44 higher)	-	34 (1 RCT)	⊕⊖⊖⊖ **Very low**[a,b,d]	Higher score indicates improved unimanual capacity.
Manual ability - not measured	-	-	-	-	-	No studies measured manual ability.
Self-care Assessed with: Pediatric Evaluation of Disability Inventory - Self-Care Functional Skills Domain Scale from: 0 to 73 Follow-up: immediately postintervention	The mean self-care in the control group was**8.04 points**	The mean self-care in the intervention group was **1.52 points higher** (3.1 lower to 6.14 higher)	-	34 (1 RCT)	⊕⊖⊖⊖ **Very low**[a,b,d]	Higher score indicates improved self-care.
Individualised measures of performance Assessed with: Canadian Occupational Performance Measure - Performance Scale from: 0 to 10	The mean individualised measure of performance in the control groups ranged from **3.07 to 3.4 points**	The mean individualised measure of performance in the intervention groups was **0.02 points lower** (0.72 lower to 0.69 higher)	-	126 (3 RCTs)	⊕⊕⊖⊖ **Low**[a,b,c]	Higher score indicates improved parent-rated occupational performance.

Follow-up: immediately post-intervention				
Adverse events	3/4 studies reported no significant adverse events resulting from CIMT. The remaining study reported 1 child receiving Hybrid CIMT had a seizure unrelated to intervention. Minor adverse events included frustrations and lack of acceptance of CIMT mitt (n = 6 children).	-	186 (4 RCTs)	-

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **MD:** Mean difference; **RCT:** randomised controlled trial.

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[a]Downgraded one level due risk of bias (all studies are at high risk of bias because it is not possible to blind personnel or participants to group allocation).
[b]Downgraded one level due to small sample size (number of participants < 400).
[c]The study protocol by Sakzewski 2015a was published and the study was retrospectively registered with ANZCTR. Secondary outcomes listed in the published protocol were not reported in the publication of study results including: Assessment of Life Habits (LIFE-H) and Cerebral Palsy Quality of Life Questionnaire (self- and parent-report). We did not downgrade the body of evidence for bimanual performance based on this finding.
[d]Downgraded one level because results are from a single study.

Summary of findings 3. Constraint induced movement therapy (CIMT) compared to dose-matched comparison for children with unilateral cerebral palsy

Constraint induced movement therapy compared to dose-matched comparison for children with unilateral cerebral palsy

Patient or population: children with unilateral cerebral palsy
Setting: mixed (home, clinic, pre-school, laboratory, camp)
Intervention: constraint induced movement therapy
Comparison: dose-matched comparison

Outcomes	Anticipated absolute effects* (95% CI)	Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments

	Risk with dose-matched comparison	Risk with constraint induced movement therapy					
Bimanual performance Assessed with: Assisting Hand Assessment - Kids Scale from: 0 to 100 Follow-up: immediately postintervention	The mean bimanual performance in the control groups ranged from **1.2 to 9.5 AHA units**	The mean bimanual performance in the intervention groups was **0.8 AHA units higher** (0.78 lower to 2.38 higher)	-	229 (7 RCTs)	⊕⊕⊖⊖ **Low[a,b,c]**	Higher score indicates improved bimanual performance.
Unimanual capacity Assessed with: Melbourne Assessment Scale from: 0 to 100 Follow-up: immediately postintervention	The mean unimanual capacity in the control groups ranged from **−0.8 to 7.1 points**	The mean unimanual capacity in the intervention groups was **1.48 points higher** (0.49 lower to 3.44 higher)	-	203 (6 RCTs)	⊕⊕⊖⊖ **Low[a,b,c]**	Higher score indicates improved unimanual capacity.
Unimanual capacity Assessed with: Quality of Upper Extremity Skills Test - Grasp Scale from: 0 to 100 Follow-up: immediately postintervention	The mean unimanual capacity in the control groups ranged from **3.7 to 10.8 points**	The unimanual capacity in the intervention group was **6.63 points higher** (2.38 lower to 15.65 higher)	-	124 (3 RCTs)	⊕⊖⊖⊖ **Very low[a,b,d]**	Higher score indicates improved unimanual capacity.
Manual ability Assessed with: ABILHAND-Kids Scale from: −10 to 10 Follow-up: immediately postintervention	The mean manual ability in the control groups ranged from **−0.08 to 0.22 logits**	The mean manual ability in the interventions group was **0.52 logits higher** (0.41 lower to 1.46 higher)	-	95 (3 RCTs)	⊕⊖⊖⊖ **Very low[a,b,d]**	Higher score indicates improved manual ability.
Self-care Assessed with: Pediatric Evaluation of Disability Inventory - Self-Care Functional Skills domain Scale from: 0 to 73 Follow-up: immediately postintervention	The mean self-care in the control groups ranged from **1.4 to 3.4 points**	The mean self-care in the intervention groups was **1.09 points lower** (2.42 lower to 0.24 higher)	-	45 (2 RCTs)	⊕⊕⊖⊖ **Low[a,b]**	Higher score indicates improved self-care.
Individualised measures of performance	The mean individualised measures of performance in the control groups	The mean individualised measures of performance in the intervention groups was**0.08 points higher**	-	191 (6 RCTs)	⊕⊖⊖⊖ **Very low[a,b,c,d]**	Higher score indicates improved occupa-

Assessed with: Canadian Occupational Performance Measure - Performance Scale from: 0 to 10 Follow-up: immediately postintervention	ranged from **1.2 to 3.4 points**	(1.29 lower to 1.46 higher)			tional performance.
Adverse events	10/15 studies reported the presence or absence of adverse events. Of these, 7 studies reported no adverse events. Facchin 2011 specifically monitored changes on the less affected limb and found no detrimental effect following CIMT. Three studies reported minor adverse events including inability to tolerate CIMT (Dong 2017) and behavioural difficulties and resistance to wearing the mitt (Smania 2009). Kirton 2016a (CIMT + r TMS) reported 11% of children who received rTMS in conjunction with CIMT experienced headaches and < 3% reported tingling and nausea.	-	569 (15 RCTs)	-	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **MD:** Mean difference; **RCT:** randomised controlled trial.

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[a]Downgraded one level due to risk of bias (all trials are at high risk of bias because it is not possible to blind personnel or participants to group allocation).
[b]Downgraded one level due to small sample size (number of participants < 400).
[c]Protocol available for Sakzewski 2011. Neurovascular changes (functional Magnetic resonance imaging, functional connectivity), and brain (re)organisation (Transcranial Magnetic Stimulation) listed in protocol but not reported or addressed in the publications. We did not downgrade the body of evidence based on this finding.
[d]Downgraded one level due to inconsistency (heterogeneity statistically significant: $P < 0.10$, $I^2 > 40\%$).

Summary of findings 4. Constraint induced movement therapy (CIMT) compared to different forms CIMT for children with unilateral cerebral palsy

Constraint induced movement therapy compared to different forms CIMT for children with unilateral cerebral palsy

Patient or population: children with unilateral cerebral palsy
Setting: mixed (home, clinic)
Intervention: Constraint induced movement therapy

Comparison: different forms CIMT

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with different forms constraint induced movement therapy	Risk with constraint induced movement therapy				
Bimanual performance Assessed with: Assisting Hand Assessment - Kids Scale from: −10.26 to 8.72 Follow-up: immediately postintervention	The mean bimanual performance in the control group was **0.84 AHA logits**	The mean bimanual performance in the intervention group was **2.19 AHA logits higher** (1.15 lower to 5.53 higher)	-	60 (2 RCTs)	⊕⊖⊖⊖ **Very low[a,c]**	Different scale units (logit scale and AHA unit scale) and different reporting (time point and change from baseline) precluded meta-analysis. Higher score indicates improved bimanual performance
Bimanual performance assessed with: Assisting Hand Assessment - Kids Scale from: 0 to 100 Follow-up: immediately postintervention	The mean bimanual performance in the control group was **5.3 AHA units**	The mean bimanual performance in the intervention group was**3.70 AHA units higher** (1.27 lower to 8.67 higher)	-			
Unimanual capacity - not measured	-	-	-	-	-	No studies measured unimanual capacity using the Melbourne Assessment 2
Unimanual capacity Assessed with: Quality of Upper Extremity Skills Test - Grasp Scale from: 0 to 100 Follow-up: immediately postintervention	The mean unimanual capacity in the control group was **−0.5 points**	The mean unimanual capacity in the intervention group was **3.70 points higher** (1.91 lower to 8.71 higher)		60 (1 RCT)	⊕⊖⊖⊖ **Very low[a,b,c]**	Higher score indicates improved bimanual performance
Manual Ability - not measured	-	-	-	-	-	No studies measured manual ability using the ABILHAND-Kids
Self-care - not measured	-	-	-	-	-	No studies measured self-care using the Pediatric Evaluation of Disability Inventory

Individualised measures of performance - not measured	-	-	-	-	No studies measured individual performance using the Canadian Occupational Performance Measure
Adverse events	2 studies reported no adverse events 1 study did not report the presence or absence of adverse events	-	94 (3 RCTs)	-	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **MD:** Mean difference; **RCT:** randomised controlled trial.

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[a]Downgraded one level due to risk of bias (all trials are at high risk of bias because it is not possible to blind personnel or participants to group allocation).
[b]Downgraded one level because results are from a single study.
[c]Downgraded one level due to small sample size (number of participants < 400).

BACKGROUND

Description of the condition

Cerebral palsy (CP) is an umbrella term, which describes "a group of permanent disorders of the development of movement and posture, causing activity limitation, that are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain" (Rosenbaum 2009, p 9). The definition also specifies that the motor disorders that characterise CP often co-exist with epilepsy; musculoskeletal, behaviour and communication problems; and difficulties with sensation, perception and cognition. CP is considered the most common cause of physical disability in childhood. In many developed countries, CP is estimated to be present in 1.9 to 2.1 children per 1000 live births (ACPR 2016).

Unilateral CP, also called hemiplegic CP, is common; 39% of children with CP in Australia have this form (ACPR 2016). Upper-limb dysfunction can range from mildly to profoundly impaired depending on the timing, site, extent and nature of the brain lesion (Holmefur 2013; Holmström 2010). Reduced ability to use the more-affected upper limb in daily activities is associated with musculoskeletal deformity, disorders of posture and movement, and impaired sensory and cognitive function (Arner 2008; Bodimeade 2013; Brown 1987; Eliasson 1995; Klingels 2012; Steenbergen 2006). The potential impact of impaired upper-limb function on restrictions to participation in daily life has resulted in extensive clinical and research endeavours, by occupational therapists and others, to devise and evaluate interventions to improve upper-limb function in this specific group of children (Beckung 2002; Fauconnier 2009; Ziviani 2008).

Upper-limb interventions employed in recent years to improve unilateral capacity, bimanual performance and task performance in children with unilateral CP include intra-muscular Botulinum toxin-A injections (Hoare 2010; Hoare 2013), casting (Autti-Rämö 2006), orthoses and Lycra splinting (Elliott 2011; Imms 2016a; Jackman 2014), surgery (Van Heest 2015), strengthening programs (Rameckers 2015), virtual reality (Snider 2010; Weiss 2014), home programs (Novak 2009), goal-directed training (Löwing 2010), action observation therapy (Kirkpatrick 2016; Sgandurra 2013), robotics (Gilliaux 2015), electrical stimulation (Xu 2015; Yıldızgören 2014), repetitive transcranial magnetic stimulation (TMS) (Gillick 2014; Kirton 2016a (CIMT + r TMS)), sensory cueing (Dong 2017), mirror therapy (Bruchez 2016), gaming (Chiu 2014) and Cognitive Orientation to daily Occupational Performance (Cameron 2017). Along with bimanual therapy (Facchin 2011; Gelkop 2015; Gordon 2007; Green 2013; Hoare 2013; Sakzewski 2011), constraint-induced movement therapy (CIMT) is one of two interventions that were developed specifically for children with unilateral CP.

Description of the intervention

The two key components that define CIMT are restraint of the less affected upper limb, with the addition of intensive, structured, upper-limb therapy (Eliasson 2014a). The definition and implementation of these two components is diverse across clinical and research environments. The types of restraints used in studies to date include splints, slings, mitts/gloves and casts. These have been applied from one hour per day to 24 hours a day, over a period of two weeks to two months or more. Intervention has been delivered individually or in groups, in the home, clinic, during inpatient programs, or novel environments such as embedded in circus- or pirate-themed camps. The nature of intensive upper-limb therapy for the more affected arm and hand has also varied greatly. Some studies reported the approach to therapy in detail, but for most, the descriptions are brief (Sakzewski 2016). Many studies used eclectic approaches or approaches that are difficult to classify according to named frameworks. Several used descriptors such as 'play' and 'involvement in functional activity', whilst some were clear that the intervention involved shaping and repetition. A few studies used goal-oriented therapy based on motor learning principles and some added bimanual therapy. Several studies did not include an intensive upper-limb therapy alongside constraint, rather they maintained the child's low-intensity pre-study therapy.

The absence of clarity around a specific definition of CIMT was addressed by an expert panel, which met to scope the state of knowledge about CIMT and to make recommendations for future clinical and research directions (Eliasson 2014a). The panel proposed four main classifications of CIMT.

- *Signature* CIMT (sCIMT), which is derived from the original model developed by Taub 2004, for adults with hemiparesis following stroke. It is defined as restraint of the unaffected upper limb for 90% of the waking day for at least two weeks, while engaging the child in intensive upper-limb therapy for three or more hours per day.
- *Modified CIMT* (mCIMT), which comprises variation to the signature model, specifically the type of restraint, nature of intensive therapy, and the hours per day and duration in weeks of the program.
- *Hybrid CIMT* (hCIMT), which is the result of efforts by clinicians and researchers to combine CIMT and bimanual forms of intervention into intervention packages. Defined as hCIMT by Eliasson 2014a, it is based on the premise that CIMT, as a unilateral intervention, may result in improved unilateral upper-limb ability, but practice of bimanual functional activities is necessary to transfer these improvements into daily life.
- *Forced use therapy*, which involves use of restraint of the less affected upper limb, without including an intensive, upper-limb intervention.

We used these definitions in this review to classify the types of CIMT across studies (See Characteristics of included studies).

How the intervention might work

CIMT used with children with unilateral CP aims to address two different but linked mechanisms to improve unilateral capacity and bimanual performance: developmental disregard and use-dependent cortical re-organisation (Taub 2007).

The term developmental disregard is used to describe behaviours of children with unilateral CP who have learned to suppress use of, and therefore to disregard, their more affected upper limb (DeLuca 2003). From an early age many children with unilateral CP discover it is more efficient and effective to complete tasks using the less affected hand, even if there is only mild impairment in the more affected limb (Kuhtz-Buschbeck 2000; Krumlinde-Sundholm 1998). Families and clinicians, particularly occupational therapists, often note a discrepancy between actual use of the limb in daily activities and the capacity for upper-limb use observed in a clinic situation (Sutcliffe 2009; Zielinski 2014a; Zielinski 2014b). Therapists, therefore, create the opportunity,

experience and environment that optimises a child's ability to use their more affected limb. This experience aims to reverse the behavioural aspect of suppression of use of the affected limb and use appropriate rewards to motivate a child to master increasingly challenging upper-limb movements and tasks. The intensive but targeted upper-limb practice in which children engage during CIMT, and which is facilitated by restraint of the less affected hand, is intended to overcome developmental disregard by counter-conditioning or reducing the suppression of motor activity (Morris 2001).

Increased and more effective use of the more affected limb during CIMT aims to induce expansion of the contralateral cortical area controlling movement of the more affected limb (Friel 2014). This activity-dependent, cortical re-organisation may serve as the neural basis for permanent increase in use of the affected limb in daily activities following treatment. Several studies provide evidence that potential exists for such activity-dependent neuroplasticity in children with unilateral CP following CIMT (Cope 2010; Juenger 2007; Manning 2015; Sutcliffe 2007; Sutcliffe 2009).

Why it is important to do this review

Four recent systematic reviews concluded that CIMT was more effective for improving upper-limb function than low intensity or standard care interventions and equally effective as an alternative, upper-limb intervention delivered at a similar dose (Dong 2013; Chen 2014; Sakzewski 2014; Chiu 2016). This latter evidence is important as it allows families choice of effective interventions to suit individual child and family preferences, needs and resources. Chen 2014 provided additional insights – reporting that effect sizes were larger immediately after intervention than at later endpoints, and that home- and clinic-based interventions resulted in larger effects than camp-based intervention. Chen 2014 also reported that type of restraint, amount of daily use, and duration of therapy did not impact outcome.

Despite the increasing clarity around the effectiveness of CIMT, more work is required to understand the minimum dose that is effective, allowing children and families to make choices that minimise burden and costs of intervention. The advent of hybrid interventions is relatively recent and a greater understanding of whether there are additive effects of combining unilateral and bimanual interventions is required. Finally, more high-quality randomosed controlled trials (RCTs) are using outcome measures that are validated for use with children with unilateral CP. This will allow for meta-analyses, which will result in trustworthy conclusions regarding the effectiveness of CIMT, allow determination of clinically important outcomes and clarification of duration of effect over time. This Cochrane Review of the most up-to-date literature addresses contemporary issues in this field of research. This is important to inform families of children with CP, service providers, clinicians and researchers of the state-of-the-art in relation to clinical applications of CIMT and directions for future research.

OBJECTIVES

To evaluate the effect of constraint-induced movement therapy (CIMT) in the treatment of the more affected upper limb in children with unilateral cerebral palsy (CP).

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trial (RCTs), cluster-RCTs or clinically controlled trials. See Differences between protocol and review.

Types of participants

Participants diagnosed with unilateral CP, aged between birth and 19 years. We only included studies involving a subset of children with unilateral CP if separate data were available for these children.

Types of interventions

In the original 2007 review (Hoare 2007a; Hoare 2007b), we used definitions of constraint-induced movement therapy (CIMT) described by Taub 2002 [pers comm]. For this update, we used the definitions outlined in a more recent expert consensus paper: signature CiMT (sCIMT); modified CIMT (mCIMT); hybrid CMIT (hCIMT); and forced use therapy (Eliasson 2014a). In this report, we use 'CIMT' as an umbrella term to encompass all specific types of CIMT (Eliasson 2014a).

We included studies that evaluated sCIMT, mCIMT, hCIMT or forced use therapy compared to usual care, conventional therapy, bimanual therapy, variations of sCIMT, mCIMT, hCIMT or forced-use therapy; alternative, upper-limb interventions; or no treatment. We also included studies where CIMT was combined with a concurrent intervention provided CIMT could be isolated as defining the intervention group from the comparison group, and that any co-intervention was implemented in each group in an identical manner. For example, an eligible comparison would be CIMT plus Botulinum toxin-A injections versus bimanual therapy plus Botulinum toxin-A injections, while an ineligible comparison would be CIMT plus bimanual therapy compared with CIMT. We excluded studies where CIMT was combined with lower-limb intervention.

Dosage of CIMT was defined as **total hours of intervention** calculated with the following formula.

Total hours of CIMT intervention = therapist-led intervention + parent-led intervention + other intervention (e.g. usual care) + forced use (Table 1).

We calculated the dosage of forced use in models of CIMT where constraint devices were worn outside of therapist- or parent-led intervention hours, such as when children wore a cast for 24 hours a day and were participating in therapy for SIX hours per day. For studies where constraint was worn for 90% of waking hours or 24 hours per day, we estimated that time involved in forced use was equivalent to 12 hours per day. In the example given above, hours of therapy per day = six hours (therapist- or parent-led) + (12 hours forced use - six hours therapist- or parent-led) = 12 hours.

To achieve the objectives of our review related to intensity of *comparison intervention*, we categorised comparison interventions according to total dosage calculated as follows.

Total hours of comparison intervention = therapist-led intervention + parent-led intervention + other intervention (e.g. usual care) (Table 2).

The following categories were included.

- *Low dose:* total hours of intervention = range 0 to 25 hours and a substantial difference from experimental-group dosage with forced-use dosage excluded.
- *High dose:* total hours of intervention > 25 hours but less than experimental-group dosage with forced-use dosage excluded.
- *Dose-matched:* experimental and comparison groups received equal dosages of therapist- + parent-led + other interventions. Time spent in forced use was excluded from the CIMT dosage for this comparison.
- *Other form of CIMT:* when CIMT was compared head-to-head with another form of CIMT such as delivered at a different dose or in a different environment.

Types of outcome measures

In the original review (Hoare 2007a; Hoare 2007b), we broadly grouped outcome measures according to the domains of the International Classification of Functioning, Disability and Health (ICF) (WHO 2001). For this review update, we categorised measures into primary or secondary outcomes, to better reflect the expected effect of CIMT (Eliasson 2014a). The goal of CIMT is to improve unilateral upper-limb ability to transfer into improved bimanual functional performance (self-care, manual ability, individual performance). The primary outcomes, therefore, focused on both bimanual and unimanual function. Secondary measures included those that CIMT may effect but are not the primary target of intervention.

We considered outcome measures ineligible for inclusion if they: 1) did not possess adequate reported validity or reliability (or both) for children with CP; 2) were standardised assessments that were invalidated because the administration or scoring was adapted; or 3) both. Ineligible measures and the reasons for ineligibility are listed in Table 3.

We deemed the following measures eligible for inclusion.

Primary outcomes

Bimanual

- Kids-Assisting Hand Assessment (Kids-AHA; Holmefur 2007; Holmefur 2009; Holmefur 2016; Krumlinde-Sundholm 2003; Krumlinde-Sundholm 2007; Krumlinde-Sundholm 2012)
- Hand Assessment for Infants (HAI) - both hands score (Krumlinde-Sundholm 2017)

Unimanual

- Melbourne Assessment of Unilateral Upper Limb Function or Melbourne Assessment 2 (Melbourne Assessment 2; Randall 2008; Randall 2012)
- Box and Blocks Test (Jongbloed-Pereboom 2013)
- Quality of Upper Extremity Skills Test (QUEST) - Dissociated movement domain (Thorley 2012)
- QUEST - Grasp domain (Thorley 2012)
- QUEST - Weight-bearing domain (Thorley 2012)
- QUEST - Protective extension domain (Thorley 2012)
- Shriner's Hospital Upper Extremity Evaluation (SHUEE; Davids 2006)
- Pediatric Motor Activity Log (PMAL) - Revised (Uswatte 2012b)
- Assessment for Infants (HAI) - Unimanual score
inde-Sundholm 2017)

Manual ability

- ABILHAND-Kids (Arnould 2004; Bleyenheuft 2017)
- Children's Hand-use Experience Questionnaire (CHEQ) - Effectiveness of grasp, Time to do task and Bothered scales only (Amer 2016; Sköld 2011)
- Birmingham Bimanual Questionnaire (Christmas 2018)

Adverse events

- We recorded adverse events for each included study (See Table 4).

Secondary outcomes

Individualised measures of performance

- Canadian Occupational Performance Measure (COPM; Carswell 2004; Cusick 2006; Cusick 2007)
- Goal Attainment Scaling (GAS; Cusick 2006)

Self-care

- Pediatric Evaluation of Disability Inventory (PEDI) - Self-Care Functional Skills domain (Feldman 1990; James 2014)
- PEDI - Self-Care Caregiver Assistance domain (Feldman 1990; James 2014)
- Functional Independence Measure for Children (WeeFIM; James 2014)

Body function

- Grip strength (for example, Jamar Dynamometer) (Klingels 2010)
- Modified Ashworth Scale - Elbow (Clopton 2005; Klingels 2010)
- Modified Ashworth Scale - Wrist (Klingels 2010)
- Two-point discrimination (Klingels 2010)
- Passive Range of Motion (PROM; Glazier 1997; Klingels 2010)
- Modified Tardieu Scale (MTS; Gracies 2010; Mackey 2004)

Participation

- Children's Assessment of Participation and Enjoyment (CAPE; Sakzewski 2007)
- Assessment of Life Habits (LIFE-H; Noreau 2007)

Quality of life

- Cerebral Palsy Quality of Life Questionnaire for Children (CP QOL) -Child/self report (Davis 2013)
- CP QOL - Child/Caregiver report (Davis 2013)
- KIDSCREEN-52 (The Kid Screen Group Europe)
- Pediatric Quality of Life Inventory (PEDSQOL™) 4.0 - Generic Core Scale (Varni 2008)
- PEDSQOL™ 3.0 - Cerebral Palsy Module (Varni 2006)
- PEDSQOL™ - Infant Scale (Varni 2011)

Parenting and family measures

- Parenting Sense of Competence Scale (Gilmore 2009)

Other

- Pediatric Arm Function Test (PAFT; Uswatte 2012a)
- School Function Assessment (SFA; Sakzewski 2007)
- Besta Scale (Rosa-Rizzotto 2014)

- Video Observations Aarts and Aarts (VOAA-DD; Aarts 2007; Aarts 2009; Houwink 2013)
- Alberta Infant Motor Scales (AIMS; Piper 1992)

Timing of outcome assessment

An additional objective for this review update was to examine the maintenance of effects of CIMT following intervention.

The primary endpoint was immediately following CIMT.

Due to variation in the timing of endpoints following CIMT, we categorised the secondary endpoints as follows.

- Two weeks to four months following CIMT
- Five to six months following CIMT
- Seven to 12 months following CIMT

Main outcomes for 'Summary of findings' table

We selected the follow-up period immediately postintervention as the time point for the 'Summary of findings' tables, as we considered this to be a time of peak effect for CIMT. Considering the available data and validity/reliability of outcome measures, two review authors (BH, MW) selected the following outcomes for inclusion through consensus.

- Bimanual, measured by the Kids-AHA (Holmefur 2007; Holmefur 2009; Holmefur 2016; Krumlinde-Sundholm 2003; Krumlinde-Sundholm 2007; Krumlinde-Sundholm 2012)
- Unimanual, measured by the Melbourne Assessment 2 (Randall 2008; Randall 2012) and the QUEST, Grasps domain (Thorley 2012)
- Manual ability, measured by the ABILHAND-Kids (Arnould 2004; Bleyenheuft 2017)
- Self-care, measured by the PEDI, Self-Care Functional Skills domain (Feldman 1990; James 2014)
- Individualised measures of performance, measured by the COPM (Carswell 2004; Cusick 2006; Cusick 2007).
- Adverse events, as reported by trial authors

Search methods for identification of studies

We ran searches up to 2006 for the previous versions of this review (Hoare 2007a; Hoare 2007b). For this update, we revised the search strategy and searched some additional databases (Differences between protocol and review). We limited the updated searches to the period 2006 onwards.

Electronic searches

We searched the databases and trials registers listed below in September 2016 and March 2018. No language restrictions were applied to the search strategy. Search strategies used for this review update are reported in Appendix 1.

- Central Register of Controlled Trials (CENTRAL; 2018, Issue 2), in the Cochrane Library (searched 26 March 2018).
- MEDLINE Ovid (1946 to March week 3 2018).
- MEDLINE In-Process & Other Non-Indexed Citations Ovid (searched 22 March 2018).
- MEDLINE Epub Ahead of Print Ovid (searched 22 March 2018).
- Embase Ovid (1974 to 21 March 2018).
- CINAHL EBSCO*host* (Cumulative Index to Nursing and Allied Health Literature; 1937 to 22 March 2018).
- PsycInfo Ovid (1967 to March week 2 2018).
- Science Citation Index - Extended Web of Science (1970 to 22 March 2018).
- PEDro (www.pedro.org.au; searched 23 March 2018).
- OTseeker (www.otseeker.com; searched 23 March 2018).
- *Cochrane Database of Systematic Reviews* (CDSR; 2018, Issue 3), part of the Cochrane Library (searched 26 March 2018).
- ClinicalTrial.gov (clinicaltrials.gov; searched 23 March 2018).
- WHO International Clinical Trials Registry Platform (WHO ICTRP; www.who.int/ictrp/en; searched 23 March 2018).
- Australian New Zealand Clinical Trials Registry (ANZCTR; www.anzctr.org.au; searched 23 March 2018).

Searching other resources

We undertook the following, additional searches.

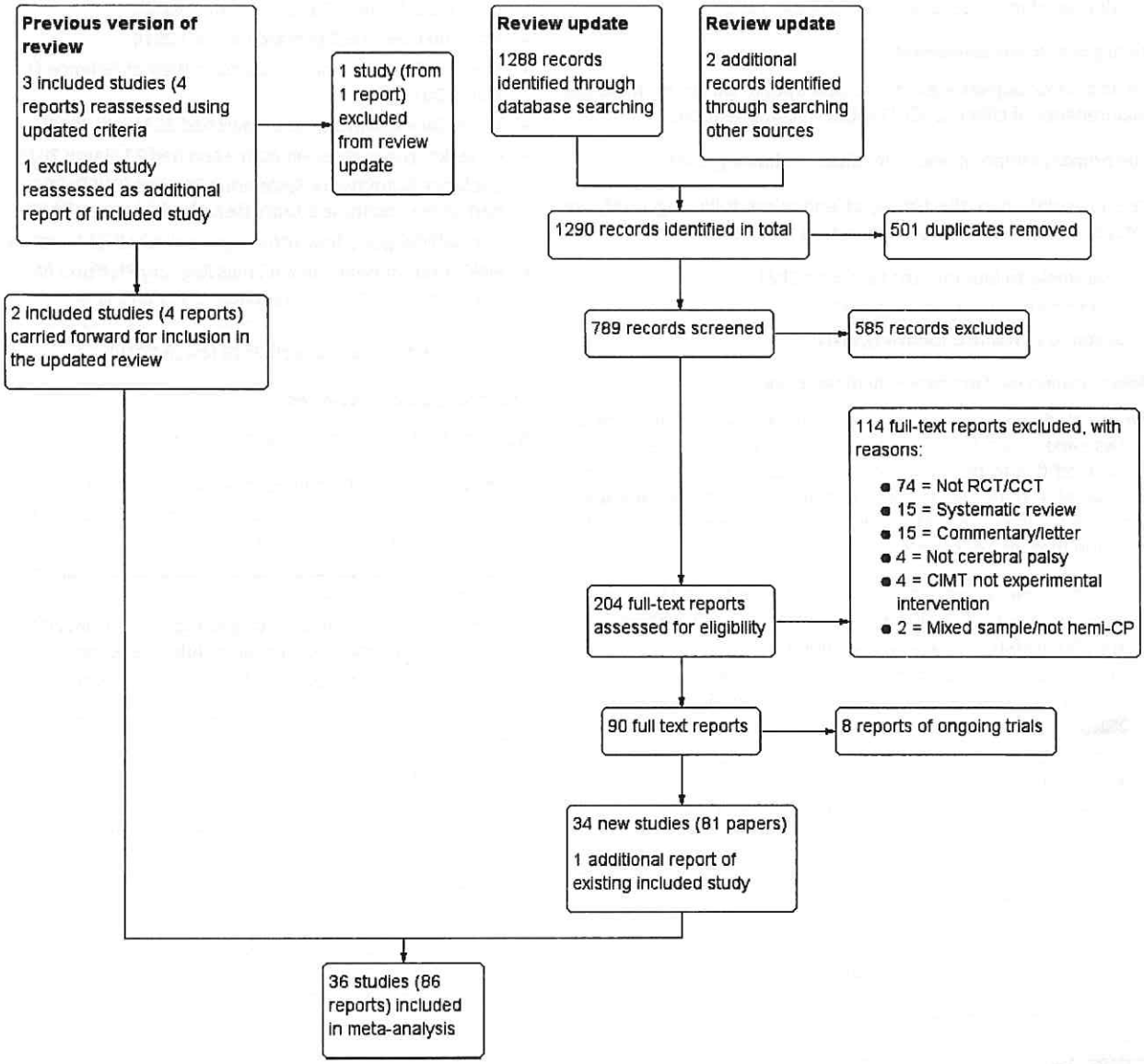
- Conversations with colleagues and key authors in this field.
- Searches of reference lists of relevant articles, systematic reviews and conference abstracts.
- Forward and backward citation searches of included studies using Google Scholar (scholar.google.com.au).
- Handsearching of the following key journals from 2007 to 2018:
  - Developmental Medicine and Child Neurology;
  - Physical and Occupational Therapy in Pediatrics;
  - Archives of Physical Medicine and Rehabilitation;
  - Journal of Child Neurology;
  - Journal of Rehabilitation Medicine;
  - Pediatric Physical Therapy;
  - American Journal of Occupational Therapy;
  - NeuroRehabilitation; and
  - Clinical Rehabilitation.
- Google Scholar (scholar.google.com.au), using the search terms 'constraint therapy' and 'cerebral palsy'.

Data collection and analysis

Selection of studies

We managed all references generated by the search strategy using EndNote (EndNote). We eliminated duplicates. Two review authors (BH and MW) independently conducted an initial screening of titles and abstracts to exclude references that clearly did not meet the inclusion criteria (Criteria for considering studies for this review). Next, we obtained full-text papers for those that provided insufficient information in the abstract to judge eligibility, and those that met the inclusion criteria. We linked multiple publications on the same study. Two review authors (BH and MW) independently evaluated the retrieved papers for relevance. We recorded the process in a PRISMA flow chart (Moher 2009); see Figure 1. We did not disagree on the inclusion/exclusion status of any abstract or article, therefore a third review author was not required. We applied no restrictions to language, date or status of publication. We sought assistance with translation, when necessary, from the *Cochrane Developmental, Psychosocial and Learning Problems* editorial team.

Figure 1. Study flow diagram



Data extraction and management

We tailored and updated the data extraction form to the requirements of this review. We piloted the form prior to commencing the original 2007 review (Hoare 2007a; Hoare 2007b). Five review authors (BH, MW, MJ, MT, CI) were paired, allocated included trials and independently extracted data from the included trials. We assembled and compared multiple publications of the same study to ensure completeness and to identify possible contradictions. If we identified contradictions, we sought additional information from the study authors. We extracted details on the study population, study environment, intervention, study methodology and outcomes of each study, to enable quality appraisal, evaluation of external validity and data analysis. Each pair of review authors resolved disagreements by discussion. We sought additional information from the study authors, if required. For cluster-randomised trials, we extracted the number of clusters in the trial, the average size of clusters, the unit of randomisation, and the statistical methods used to analyse the trial. We also recorded estimates of the intra-cluster correlation (ICC) coefficient for each outcome when they were reported.

Assessment of risk of bias in included studies

The pairs of review authors independently assessed the risk of bias of each trial, according to the criteria in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a), and set out in Appendix 2, across the following domains: sequence generation; allocation concealment; blinding; incomplete outcome data; selective reporting; and other sources of bias. This assessment consisted of two parts: (1) a succinct description of the evidence used in making assignation of study quality for each domain, which included verbatim quotes from the paper or correspondence with the trial author(s), or a comment from the review author about procedures used to avoid bias, or both; and (2) an assessment of risk of bias (resulting in assignment of a judgement of 'low', 'high' or

'unclear' risk of bias) for each of the domains. We contacted the trial authors for additional information if the publication did not provide adequate information to enable informed ratings. Discrepancies within the pairs were resolved by discussion. A third review author was consulted to resolve disagreement, if required. In the event that the review authors had undertaken the studies included in the review, independent review authors, who were not associated with these studies, extracted the data, assessed the risk of bias and populated the 'Risk of bias' tables.

Measures of treatment effect

Continuous data

We followed the *Cochrane Handbook for Systematic Reviews of Interventions* preferred method for handling continuous variables (Deeks 2011) and methods used in the original review (Hoare 2007a; Hoare 2007b). For primary outcomes, we assessed mean change scores and the standard deviation (SD) of the mean difference (MD), as opposed to comparing means and SD at specific time points. This approach considers differences in baseline performance, which is an issue for research involving small sample sizes and heterogeneous populations such as children with CP. We contacted the authors of included studies to obtain additional data to enable use of mean change scores for analysis, if required. When mean change scores and the SD of the MD were not available, we used the mean and SD at each time point (Deeks 2011). We used the MD and relevant 95% confidence intervals (CIs) when trials used the same rating scale or test to pool results across studies for an outcome. We used the standardised mean difference (SMD) and relevant 95% CI to pool trials that used different rating scales or tests.

Dichotomous data

No study included dichotomous data. We outline methods for handling dichotomous data in future updates of the review in the Differences between protocol and review section and Table 5.

Unit of analysis issues

Cross-over trials

CIMT aims to have a lasting effect and we anticipated that effects would have carry-over beyond a wash-out period into the cross-over period (Charles 2006). Therefore, as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011c), we included data from the first intervention period only for RCTs using a cross-over design (Eliasson 2011; Smania 2009; Taub 2004).

Cluster-randomised trials

For cluster-randomised trials that were randomised using clusters, we extracted the number of clusters in the trial, the average size of clusters, and the unit of randomisation. Where possible, we documented the statistical methods used to analyse the trial. We examined the methods for adjustments for clustering or other covariates. Where study authors had adjusted results for clustering, we extracted means, SD, and the number of participants in each treatment group, and included these data in the meta-analyses. Where study authors had not adjusted results for clustering, we followed the methods outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b).

Studies with multiple treatment groups

For multi-arm trials we either selected one pair of interventions that most closely matched our inclusion criteria and excluded the others, or we grouped the data so the only difference between the groups was CIMT.

Dealing with missing data

We attempted to contact the trial investigators of included studies when there was incomplete reporting of data or additional data were required (e.g. requesting change data). We reported our correspondences, and outcomes, in the Characteristics of included studies tables. When authors of included studies were unable to provide additional data, we included all of the data that were available in the review. Where data such as SD were not available, we used the CI and group size to calculate a SD using the calculator and methods according to Higgins 2011c. We assessed the risk of bias arising from incomplete outcome data as part of the overall 'Risk of bias' assessment (Assessment of risk of bias in included studies).

Assessment of heterogeneity

We pooled study data in a meta-analysis for outcomes with data from at least two homogenous studies (studies that investigated the effects of CIMT on similar populations and reported similar outcomes). We explored heterogeneity initially through visual exploration of the forest plots and considered the I^2 statistic, which describes the percentage of variability in the effect estimates due to heterogeneity (Higgins 2002). In addition, we considered the Tau^2 statistic for each meta-analysis, and compared the magnitude of heterogeneity with the distribution values for general physical health and adverse event and pain and quality of life/functioning – nonpharmacologic (median = 0.050, 95% CI 0.00 to 4.00). We considered heterogeneity in the meta-analysis to be substantial when the Tau^2 value was greater than 0.05 (Rhodes 2015).

Assessment of reporting biases

We considered the possible influence of publication and small study biases on review findings. In the current review, if we suspected or found direct evidence for selective outcome reporting, we contacted study authors for additional information.

Data synthesis

Comparisons of interest were CIMT versus low dose, high dose and dose-matched, and CIMT other forms of CIMT. We did not pool data from these four comparisons together in a single meta-analysis. We believe that the effect sizes for each of these comparisons are likely to vary considerably and that it is not theoretically justifiable to include interventions with vastly different treatment dosages in one comparison group. In the original 2007 review (Hoare 2007a; Hoare 2007b), we planned to calculate pooled effects using a fixed-effect model across trials, using the same outcome in similar populations. However, due to the limited number of included trials, no pooled analyses were possible. For this update, we used a random-effects model for each meta-analysis, as we could not assume the effects being estimated in the different studies were identical due to the nature of CIMT provided (e.g. difference in treatment dosage, restraint type etc.) (DerSimonian 1986). We considered separate meta-analyses for the timing of follow-up, including immediately postintervention (zero to two weeks), two weeks to four months, five to six months, and seven to 12 months

following CIMT. For several outcomes we were not able to pool data in a meta-analysis because data were only available from a single study or change from baseline data were not available. For these studies, we presented data (mean with SD, or mean difference (MD) with 95% CI) from the CIMT and comparison groups in tables, for a narrative description of the results.

Two review authors (BH, MW) used the GRADE approach to assess the quality of the body of evidence for each outcome in each comparison (Guyatt 2008). We reported our GRADE ratings for all outcomes for comparisons of CIMT versus low dose, CIMT versus high dose and CIMT versus dose-matched, and a comparison of different forms of CIMT in the Effects of interventions section. We also presented GRADE ratings for outcomes where there were sufficient data to conduct meta-analyses for comparisons in 'Summary of findings' tables, which we constructed using GRADEpro (GradePro GDT 2015; Schünemann 2013). Consistent with criteria applied by (Ryan 2017), and to ensure consistency of GRADE judgements, we applied the criteria below for all key comparisons.

- Limitations of studies: downgrade once if less than 75% of included studies are at low risk of bias across all 'Risk of bias' domains.
- Inconsistency: downgrade once if heterogeneity is statistically significant ($P < 0.10$) and $I^2 > 40\%$, or if data were from a single study only.
- Indirectness: downgrade once if more than 50% of the participants are outside the target group.
- Imprecision: downgrade once if fewer than 400 participants for continuous data and fewer than 300 events for dichotomous data (Guyatt 2011).
- Publication bias: downgrade where there is direct evidence of publication bias.

We summarised the adverse events in Table 4.

Subgroup analysis and investigation of heterogeneity

We were unable to conduct any subgroup analyses due to the small number of studies in each comparison. These have been archived in Table 5 for use in future updates of this review, should data permit.

Sensitivity analysis

We assessed the influence of our analysis model by re-analysing data using a fixed-effect model instead of a random-effects model for all outcomes included in a pooled analyses, as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions section* (Sterne 2011).

RESULTS

Description of studies

Results of the search

For the previous version of this review (Hoare 2007a; Hoare 2007b), we screened 214 references and identified three included studies. The database searches for this update found 1288 records; we found two additional records by searching Google Scholar. After removing obvious duplicates, we screened the titles and abstracts of 789 records. Of these, we excluded 585 irrelevant records and obtained 204 full-text reports for further scrutiny. Two review authors (BH, MW) independently examined the full-text versions and agreed to include 34 new studies (from 81 reports) of sCIMT, mCIMT, hybrid therapy or forced use, plus one additional report of a study already included, making a total of 36 included studies from 86 reports. We also identified eight ongoing studies (Ongoing studies).

Four studies were published in Persian with English abstracts (Abootalebi 2010; Gharib 2010; Hosseini 2010; Sabour 2012). We later identified an English manuscript for Hosseini 2010. The remaining three studies were assessed and data extracted by two independent Persian speaking health professionals (Associate Professor Mehdi Rassafiani and Dr Fakher Rahim).

See Figure 1 for the study selection process.

Included studies

Three randomised or controlled clinical trials of CIMT, with a total of 70 participants, were included in the original review (Eliasson 2005; Sung 2005; Taub 2004). We retained two of these studies (Sung 2005; Taub 2004). We excluded the trial by Eliasson 2005 from this update as no randomisation was used and we did not consider the methods to meet the requirements for a controlled clinical trial as defined in Box 6.3.a of the *Cochrane Handbook for Systematic Reviews of Interventions* (Lefebvre 2011). This review therefore includes 36 original and independent studies (Aarts 2010; Abd El-Kafy 2014; Abootalebi 2010; Al-Oraibi 2011; Charles 2006; Chen 2014; Choudhary 2013; Christmas 2018; de Brito Brandão 2010; DeLuca 2012; Deppe 2013; Dong 2017; Eliasson 2011; Eliasson 2018; Eugster-Buesch 2012; Facchin 2011; Gelkop 2015; Gharib 2010; Gordon 2011; Hoare 2013; Hosseini 2010; Kirton 2016a (CIMT + r TMS); Rostami 2012a; Rostami 2012b; Sabour 2012; Sakzewski 2011; Sakzewski 2015a; Sakzewski 2015b; Smania 2009; Sung 2005; Taub 2004; Taub 2011; Wallen 2011; Xu 2012; Yu 2012; Zafer 2016). The 36 trials included a total of 1264 participants and took place between 2004 and 2018. Details for each study are provided in Characteristics of included studies tables.

Design

Of the 36 included studies, 35 were randomised controlled trials (RCTs) and one was a cluster-RCT (Facchin 2011). The study by Facchin 2011 included 105 participants across 21 rehabilitation sites where each participating clinical centre was randomised to one of three interventions (e.g. centre A was randomised to deliver mCIMT; centre D was randomised to deliver Bimanual Intensive Rehabilitation programme and so on). In this way, all children enrolled in a particular clinical centre participated in the intervention randomly assigned to that centre. The study authors report that no significant differences among inter- and intra-cluster variabilities were observed in children enrolled in the trial. We therefore included the data in meta-analyses.

Most trials compared two groups, that is, CIMT versus a comparison intervention. Three trials included a three-group design (Dong 2017; Facchin 2011; Xu 2012) and two trials included a four-group design (Kirton 2016a (CIMT + r TMS); Rostami 2012b).

One trial (Xu 2012) included three groups comparing mCIMT +Functional Electrical Stimulation (FES), mCIMT alone and occupational therapy (OT) alone. As the mCIMT+FES group combined two distinct interventions we did not consider this group to be sufficiently similar to the mCIMT alone group to be combined

to create a single pair-wise comparison. Therefore, we excluded this group from comparison and selected the groups that most closely matched our inclusion criteria (mCIMT alone and OT alone).

Facchin 2011 included three groups comparing mCIMT with a high-dose, bimanual, intensive rehabilitation group and a low-dose, traditional rehabilitation group. These groups were all deemed to meet our inclusion criteria and were analysed in separate analyses. Therefore, combining data from the two comparison groups was not required.

Rostami 2012b included a four-group design including mCIMT +Virtual Reality (VR), VR alone, mCIMT alone and a low-dose comparison. The nature of these interventions allowed CIMT to be isolated from co-interventions across three comparisons. This included mCIMT(+VR) versus dose-matched VR, mCIMT versus dose-matched VR and mCIMT versus low-dose usual care. No data were available for analysis however.

The study by Kirton 2016a (CIMT + r TMS) included a four-group design comparing CIMT+ repetitive Transcranial Magnetic Stimulation (rTMS), intensive motor learning therapy + rTMS, CIMT +sham rTMS and intensive motor learning therapy+sham rTMS. The nature of these groups allowed CIMT to be isolated from co-interventions across two comparisons: CIMT(+rTMS) versus dose-matched intensive motor learning therapy (+rTMS) and CIMT(+ sham rTMS) versus dose-matched motor learning (+ sham rTMS). To allow analysis of data from these two comparisons we set up two study IDs for this study. Kirton 2016a (CIMT + r TMS) examines the comparison of CIMT(+ rTMS) versus dose-matched intensive motor learning therapy (+ rTMS) and Kirton 2016b (CIMT + sham TMS) examines the comparison CIMT(+ sham) versus dose-matched intensive motor learning therapy (+ sham).

The type of CIMT provided in the studies included the following.

- Signature CIMT used in two studies (Kirton 2016a (CIMT + r TMS); Taub 2004).
- Modified CIMT used in 24 studies (Abd El-Kafy 2014; Al-Oraibi 2011; Chen 2014; Choudhary 2013; Christmas 2018; Dong 2017; Eliasson 2011; Eliasson 2018; Eugster-Buesch 2012; Facchin 2011; Gelkop 2015; Gordon 2011; Hoare 2013; Hosseini 2010; Rostami 2012a; Rostami 2012b; Sakzewski 2011; Sakzewski 2015b; Smania 2009; Sung 2005; Wallen 2011; Xu 2012; Yu 2012; Zafer 2016).
- Hybrid CIMT used in 10 studies (Aarts 2010; Abootalebi 2010; Charles 2006; de Brito Brandão 2010; DeLuca 2012; Deppe 2013; Gharib 2010; Sabour 2012; Sakzewski 2015a; Taub 2011).

We identified no studies of forced-use therapy alone. However, in 11 studies, children used constraints to limit less affected upper-limb function for periods of time in addition to the times they were engaged in structured therapy (Abootalebi 2010; Christmas 2018; de Brito Brandão 2010; DeLuca 2012; Rostami 2012a; Rostami 2012b; Smania 2009; Sung 2005; Taub 2004; Taub 2011; Zafer 2016).

We classified the comparison groups as follows.

- Low-dose comparison used in 17 studies (Abootalebi 2010; Al-Oraibi 2011; Charles 2006; Choudhary 2013; de Brito Brandão 2010; Dong 2017; Eliasson 2011; Eliasson 2018; Eugster-Buesch 2012; Facchin 2011; Gharib 2010; Hosseini 2010; Rostami 2012b; Sabour 2012; Taub 2004; Taub 2011; Yu 2012).
- High-dose comparison used in five studies (Chen 2014; DeLuca 2012; Hoare 2013; Wallen 2011; Sakzewski 2015a).
- Dose-matched comparison used in 17 studies (Aarts 2010; Abd El-Kafy 2014; Deppe 2013; Dong 2017; Facchin 2011; Gelkop 2015; Gordon 2011; Kirton 2016a (CIMT + r TMS); Kirton 2016b (CIMT + sham TMS); Rostami 2012a; Rostami 2012b; Sakzewski 2011; Sakzewski 2015b; Smania 2009; Sung 2005; Xu 2012; Zafer 2016).
- Different form of CIMT used in three studies (Christmas 2018; DeLuca 2012; Rostami 2012a).

Of the 36 included trials, we were able to undertake 40 comparisons. Multiple comparisons were possible for three studies (Dong 2017; Facchin 2011; Rostami 2012b), due to multi-group designs. The trial by Kirton 2016a (CIMT + r TMS) allowed two independent comparisons in the same comparison group (i.e. CIMT versus dose-matched) (Kirton 2016a (CIMT + r TMS) and Kirton 2016b (CIMT + sham TMS)). We set up two study IDs to allow analysis of data from both comparisons: Kirton 2016a (CIMT + r TMS) examines the comparison of CIMT(+ rTMS) versus dose-matched intensive motor learning therapy (+ rTMS), and Kirton 2016b (CIMT + sham TMS) examines the comparison CIMT(+ sham) versus dose-matched intensive motor learning therapy (+ sham).

We undertook the following comparisons.

- CIMT versus low dose (17 comparisons: Abootalebi 2010; Al-Oraibi 2011; Charles 2006; Choudhary 2013; de Brito Brandão 2010; Dong 2017; Eliasson 2011; Eliasson 2018; Eugster-Buesch 2012; Facchin 2011; Gharib 2010; Hosseini 2010; Rostami 2012b; Sabour 2012; Taub 2004; Taub 2011; Yu 2012).
- CIMT versus high dose (four comparisons: Chen 2014; Hoare 2013; Sakzewski 2015a; Wallen 2011).
- CIMT versus dose-matched (16 comparisons (15 studies): Aarts 2010; Abd El-Kafy 2014; Deppe 2013; Dong 2017; Facchin 2011; Gelkop 2015; Gordon 2011; Kirton 2016a (CIMT + r TMS); Kirton 2016b (CIMT + sham TMS); Rostami 2012b; Sakzewski 2011; Sakzewski 2015b; Smania 2009; Sung 2005; Xu 2012; Zafer 2016).
- CIMT versus different form of CIMT (three comparisons: Christmas 2018; DeLuca 2012; Rostami 2012a).

Sample sizes

There was considerable variation in sample size between studies. The 36 included studies randomised 1264 participants with unilateral cerebral palsy (CP), with sample sizes ranging from 11 participants in Smania 2009 to 105 participants in Facchin 2011 (mean = 35; median = 31). Ten (28%) studies included sample sizes of fewer than 20 participants.

Participant characteristics

Across the 36 included studies, participant characteristics were inconsistently reported using data for either the whole sample or following dropout. Of the 1195 participants for whom data were reported, 633 (53%) were boys and 562 were girls. Eight studies did not report side of hemiplegia. For the remaining 28 trials, 471 participants (47%) had left hemiplegia and 529 right hemiplegia. One study did not report the age of participants (Sabour 2012). Of the remaining 35 studies, the mean age of participants was 5.96 years (SD 1.82), range three months to 19.8 years.

Twelve studies, including a total of 415 participants, classified children using the Manual Ability Classsification System (MACS) Eliasson 2006. Of the 425 children, 119 (28.6%) were classified at MACS I, 245 (59.1%) at MACS II, 49 (11.8%) at MACS III and 2 (0.05%) at MACS IV. Eight studies including a total of 383 participants classified children using the Gross Motor Function Classification System (GMFCS) Palisano 2008; 250 (65.3%) were classified at GMFCS I, 132 (34.5%) at GMFCS II and 1 at GMFCS III.

The most common criteria for inclusion of participants were active range of motion at the wrist/fingers in the more affected upper limb and adequate intellectual ability. Sixteen studies specified that participants required the ability to extend the wrist at least 20° and the fingers at least 10° from full flexion at the metacarpophalangeal joints (Abd El-Kafy 2014; Abootalebi 2010; Charles 2006; Chen 2014; Deppe 2013; Dong 2017; Gelkop 2015; Gordon 2011; Hosseini 2010; Rostami 2012a; Rostami 2012b; Sabour 2012; Wallen 2011; Xu 2012; Yu 2012; Zafer 2016). A further six studies included only those children who could grasp or release with the more affected hand (Eugster-Buesch 2012; Gelkop 2015; Gharib 2010; Sakzewski 2015b; Smania 2009; Hoare 2013). The study by Eliasson 2011 specifically included participants with any severity level of decreased hand function. In 16 studies, children needed to be able to follow simple or one-stage commands (Abd El-Kafy 2014; Abootalebi 2010; Choudhary 2013; de Brito Brandão 2010; DeLuca 2012; Dong 2017; Eliasson 2011; Eugster-Buesch 2012; Gharib 2010; Hoare 2013; Rostami 2012a; Sakzewski 2011; Smania 2009; Wallen 2011; Xu 2012; Yu 2012). Two studies required participants to have normal intellectual function (Al-Oraibi 2011; Gelkop 2015), and four studies specified children required an intellectual quotient (IQ) of > 70, measured using standardised assessment tools (Charles 2006; Gordon 2011; Hosseini 2010; Sabour 2012).

Twenty studies excluded participants if they had upper-limb Botulinum toxin-A injections in the six months prior to commencing CIMT (Abd El-Kafy 2014; Abootalebi 2010; Charles 2006; Chen 2014; Choudhary 2013; de Brito Brandão 2010; DeLuca 2012; Deppe 2013; Dong 2017; Facchin 2011; Gelkop 2015; Gordon 2011; Hoare 2013; Rostami 2012a; Rostami 2012b; Sabour 2012; Sakzewski 2011; Sakzewski 2015b; Taub 2011; Xu 2012). Seventeen studies also excluded children who had recent or prior upper-limb surgery (Abd El-Kafy 2014; Abootalebi 2010; Charles 2006; Choudhary 2013; Deppe 2013; Eliasson 2011; Gharib 2010; Gordon 2011; Hoare 2013; Hosseini 2010; Rostami 2012a; Rostami 2012b; Sabour 2012; Sakzewski 2015a; Sakzewski 2015b; Sung 2005; Xu 2012). Studies also excluded participants due to current or uncontrolled seizures (14 studies), visual impairment (14 studies), muscle contractures or modified Ashworth Scale scores of > 3 (11 studies), or hearing impairment (four studies). Four studies did not report exclusion criteria (Al-Oraibi 2011; Eugster-Buesch 2012; Taub 2004; Xu 2012).

Location of studies

Studies were conducted across 19 countries. Five studies were conducted in Australia (Hoare 2013; Sakzewski 2011; Sakzewski 2015a; Sakzewski 2015b; Wallen 2011) and five in the USA (Charles 2006; DeLuca 2012; Gordon 2011; Taub 2004; Taub 2011). Other countries with multiple studies included Iran (four studies: Abootalebi 2010; Gharib 2010; Hosseini 2010; Sabour 2012), Italy (two studies: Facchin 2011; Smania 2009), China (two studies: Dong 2017; Xu 2012), Korea (two studies: Sung 2005; Yu 2012), and Sweden (two studies: Eliasson 2011; Eliasson 2018). Single studies were completed in the Netherlands (Aarts 2010), Germany (Deppe 2013), Switzerland (Eugster-Buesch 2012), Brazil (de Brito Brandão 2010), Canada (Kirton 2016a (CIMT + r TMS)), Jordan (Al-Oraibi 2011), Egypt (Abd El-Kafy 2014), Israel (Gelkop 2015), Taiwan (Chen 2014), India (Choudhary 2013) and Pakistan (Zafer 2016).

CIMT mode of delivery

Dosage of CIMT

See summary of CIMT dosage in Table 1.

When the total amount of CIMT was calculated (*therapist-led intervention + parent-led intervention + other intervention (e.g. usual care) + forced use),* the mean number of hours provided across included studies was 129 hours (range 20 hours (Yu 2012) to 504 hours (Christmas 2018; Sung 2005). When the forced use component was removed, the average total dosage was 79 hours (range six hours (Sung 2005) to 210 hours (Facchin 2011).

The average length of CIMT programs was five weeks, ranging from one week (Sakzewski 2015b) to 12 weeks (Eliasson 2018). The duration of daily intervention sessions ranged from 0.5 hours (Eliasson 2018; Sung 2005) to eight hours per day (Kirton 2016a (CIMT + r TMS)). Frequency of therapist- and/or parent-led intervention sessions ranged from twice weekly (Smania 2009; Sung 2005) to seven days per week (Abootalebi 2010; Chen 2014; DeLuca 2012; Eliasson 2011; Eugster-Buesch 2012; Gharib 2010; Hoare 2013; Wallen 2011).

All studies provided information on the amount of therapist-led intervention provided. On average, 56 hours of CIMT was provided by therapists during a CIMT program (range 0 to 126 hours). In three studies, implementation of CIMT was parent-led (Eliasson 2011; Eliasson 2018; Eugster-Buesch 2012).

Nine studies did not provide information about if, or how much, parent-led intervention was provided in the CIMT protocol (Abootalebi 2010; Al-Oraibi 2011; Gharib 2010; Hosseini 2010; Rostami 2012b; Smania 2009; Sung 2005; Taub 2011; Yu 2012). Ten studies did not include parent-led intervention sessions. Where reported, there was an average dosage of 34 hours of parent-led intervention, ranging from 10 (Charles 2006; Kirton 2016a (CIMT + r TMS); Rostami 2012a; Xu 2012) to 152 hours (Hoare 2013).

In seven studies, usual care continued during the CIMT intervention period (Abootalebi 2010; Choudhary 2013; de Brito Brandão 2010; Eugster-Buesch 2012; Gharib 2010; Rostami 2012b; Sabour 2012). Mean total dosage of other interventions across these studies was six hours, ranging from two hours (Eugster-Buesch 2012) to 14 hours (Gelkop 2015).

CIMT protocols in 11 studies included forced use defined as use of a constraint outside of therapist- or parent-led intervention (Abootalebi 2010; Christmas 2018; de Brito Brandão 2010; DeLuca 2012; Rostami 2012a; Rostami 2012b; Smania 2009; Sung 2005; Taub 2004; Taub 2011; Zafer 2016). The average total dose of forced use was 161 hours, ranging from 22 hours (Zafer 2016) to 498 hours (Sung 2005).

Type of constraint

A range of methods were used to constrain use of the less affected upper limb. The most common included a mitt/glove (Al-Oraibi 2011; Chen 2014; Eliasson 2011; Eliasson 2018; Gelkop 2015; Hoare 2013; Sakzewski 2011; Sakzewski 2015a; Sakzewski 2015b; Smania

2009; Wallen 2011), or a sling (Aarts 2010; Abd El-Kafy 2014; Abootalebi 2010; Charles 2006; Choudhary 2013; de Brito Brandão 2010; Gordon 2011; Sabour 2012; Yu 2012; Zafer 2016). Each method was used in 11 studies. Seven studies used a splint (Dong 2017; Facchin 2011; Gharib 2010; Hosseini 2010; Rostami 2012a; Rostami 2012b; Xu 2012), seven used a cast (Christmas 2018; DeLuca 2012; Eugster-Buesch 2012; Kirton 2016a (CIMT + r TMS); Sung 2005; Taub 2004; Taub 2011), and the remaining study used a bandage to fix the child's arm to their trunk (Deppe 2013).

Therapy provider

The delivery of CIMT was undertaken by a diverse range of therapists, parents, teachers or other interventionists. Most commonly, CIMT was delivered by a combination of therapists and parents (17 studies - Aarts 2010; Abd El-Kafy 2014; Abootalebi 2010; Al-Oraibi 2011; Chen 2014; Choudhary 2013; Eliasson 2011; Eliasson 2018; Facchin 2011; Gharib 2010; Hoare 2013; Kirton 2016a (CIMT + r TMS); Taub 2004; Taub 2011; Wallen 2011; Xu 2012; Zafer 2016), followed by delivery by therapists alone (11 studies - de Brito Brandão 2010; DeLuca 2012; Deppe 2013; Dong 2017; Gelkop 2015; Rostami 2012a; Rostami 2012b; Sabour 2012; Smania 2009; Sung 2005; Yu 2012), parents alone (one study - Eugster-Buesch 2012), therapist and interventionists (physiotherapists, students and volunteers, three studies - Sakzewski 2011; Sakzewski 2015a; Sakzewski 2015b), or parents and unspecified interventionists ("trained interventionists", graduate and undergraduate students, teachers; three studies - Charles 2006; Christmas 2018 Gordon 2011).

Therapy location

Most often CIMT was delivered in clinical treatment centres (nine studies) (Aarts 2010; Chen 2014; Choudhary 2013; de Brito Brandão 2010; Deppe 2013; Rostami 2012b; Sabour 2012; Sung 2005; Yu 2012), or a combination of clinical treatment centres and home (eight studies) (Abd El-Kafy 2014; Abootalebi 2010; Al-Oraibi 2011; Facchin 2011; Gharib 2010; Hoare 2013; Wallen 2011; Xu 2012). Other treatment environments included home-based (Eliasson 2018; Eugster-Buesch 2012; Rostami 2012a; Taub 2004; Zafer 2016), home and community settings (Christmas 2018; DeLuca 2012; Taub 2011), home and pre-school (Eliasson 2011), school (Dong 2017; Gelkop 2015), theme camps (Sakzewski 2011; Sakzewski 2015a; Sakzewski 2015b), and camps and home (Kirton 2016a (CIMT + r TMS)).

CIMT was most commonly delivered to children individually (21 studies) (Abd El-Kafy 2014; Abootalebi 2010; Al-Oraibi 2011; Christmas 2018; de Brito Brandão 2010; DeLuca 2012; Deppe 2013; Dong 2017; Eliasson 2011; Eliasson 2018; Eugster-Buesch 2012; Facchin 2011; Gharib 2010; Hoare 2013; Kirton 2016a (CIMT + r TMS); Kirton 2016b (CIMT + sham TMS); Sung 2005; Taub 2004; Taub 2011; Wallen 2011; Zafer 2016). Eleven studies implemented CIMT in group-based models (Aarts 2010; Charles 2006; Chen 2014; Choudhary 2013; Gordon 2011; Sabour 2012; Sakzewski 2011; Sakzewski 2015a; Sakzewski 2015b; Xu 2012; Yu 2012). Two studies combined both delivery methods (Gelkop 2015; Kirton 2016a (CIMT + r TMS)).

Twenty-two studies reported the provision of home programs for implementation of CIMT. Ten studies reported no home program being provided (de Brito Brandão 2010; DeLuca 2012; Deppe 2013; Dong 2017; Sabour 2012; Sakzewski 2011; Sakzewski 2015a; Sakzewski 2015b; Smania 2009; Sung 2005), and four studies did not specify whether a home program was provided (Gelkop 2015; Hosseini 2010; Rostami 2012b; Yu 2012).

Models of practice

Equal numbers of studies reported using shaping (11 studies) (Aarts 2010; Abd El-Kafy 2014; Charles 2006; Chen 2014; Choudhary 2013; de Brito Brandão 2010; DeLuca 2012; Deppe 2013; Kirton 2016a (CIMT + r TMS); Taub 2004; Taub 2011) or motor learning theory (12 studies) (Eliasson 2011; Eliasson 2018; Facchin 2011; Gelkop 2015; Gordon 2011; Hoare 2013; Sabour 2012; Sakzewski 2011; Sakzewski 2015a; Sakzewski 2015b; Smania 2009; Wallen 2011) to guide the implementation of CIMT. Other models of practice were described as fine/gross motor activities (seven studies) (Christmas 2018; Dong 2017; Rostami 2012a; Rostami 2012b; Sung 2005; Xu 2012) and motor training (Al-Oraibi 2011). The model of practice was not described in four studies (Abootalebi 2010; Eugster-Buesch 2012; Gharib 2010; Yu 2012).

Fidelity

Six studies provided a detailed description of the intervention model and implementation methods in published study protocols (Eliasson 2018; Facchin 2011; Hoare 2013; Sakzewski 2011; Sakzewski 2015a; Sakzewski 2015b). Kirton 2016a (CIMT + r TMS) provided supplementary information detailing the intervention using the Template for Intervention Description and Replication (TIDieR) checklist and guide (Hoffmann 2014). We did not attempt to obtain unpublished intervention protocols from other studies. Only a single study (DeLuca 2012) reported methods to evaluate treatment fidelity. This involved the following: "The therapists in the study videotaped their intervention activities 3 times each week (for a total of 12 sessions) to evaluate treatment fidelity. They also maintained systematic daily treatment logs that included the specific skills and activities practiced, frequency of administration, any behavioral or logistical challenges encountered, and daily progress observed. The experienced clinical research staff at University of Alabama monitored fidelity by reviewing and analysing the videotapes and intervention logs using a fidelity checklist developed for the study" (Case-Smith 2012, p 18/19).

Comparison interventions

Low-dose comparison groups

Seventeen studies employed a low-dose comparison intervention (Abootalebi 2010; Al-Oraibi 2011; Charles 2006; Choudhary 2013; de Brito Brandão 2010; Dong 2017; Eliasson 2011; Eliasson 2018; Eugster-Buesch 2012; Facchin 2011; Gharib 2010; Hosseini 2010; Rostami 2012b; Sabour 2012; Taub 2004; Taub 2011; Yu 2012). In most of these studies, insufficient information was provided about the specific nature of the intervention. Thirteen of these studies described the comparison intervention as occupational therapy, usual care or conventional/traditional therapy (Abootalebi 2010; Choudhary 2013; de Brito Brandão 2010; Dong 2017; Eliasson 2011; Eugster-Buesch 2012; Facchin 2011; Gharib 2010; Rostami 2012b; Sabour 2012; Taub 2004; Taub 2011; Yu 2012); nine of which specified that intervention was delivered by occupational therapists (suggesting upper-limb intervention was included). The remainder of the interventions were delivered by physiotherapists (n = 1) or did not specify the intervention providers. Other comparison interventions were described as neuro-developmental therapy (NDT) (two studies: Al-Oraibi 2011; Hosseini 2010) and infant massage (one study: Eliasson 2011). Most studies provided very few details of the nature of low-dose

comparison interventions. Insufficient information was given by Hosseini 2010 to name the low-dose intervention.

The average total dose for the 13 studies which reported dosage information was 7.9 hours (range 0 to 16 hours). None of these studies, however, reported information about the dose of home program included in the intervention. Four studies did not specify intervention dosage (Eliasson 2011; Eliasson 2018; Eugster-Buesch 2012; Hosseini 2010), and one specified that no comparison intervention was provided (Charles 2006). For 12 of the studies which provided information on intervention frequency, low-dose interventions were carried out over two to 10 weeks with therapists from zero to seven days per week in sessions of 20 to 60 minutes per day. Three studies specified that no home program was included (Charles 2006; de Brito Brandão 2010; Dong 2017), two included a home program but gave no information on dose (Choudhary 2013; Eliasson 2018) and the remaining 12 studies did not mention the inclusion of a home program.

High-dose comparison groups

Four studies employed a high-dose comparison intervention (Chen 2014; Hoare 2013; Sakzewski 2015a; Wallen 2011). These interventions were intensive, individualised occupational therapy (Sakzewski 2015a; Wallen 2011), bimanual occupational therapy (Hoare 2013), or intensive traditional rehabilitation delivered by physiotherapists (Chen 2014).

The average total dose, including therapist delivered and home program hours for the four high-dose comparison interventions was 37.5 hours (range 30 to 45 hours). These interventions were carried out with therapists over four to eight weeks, one to two days per week, in sessions of 45 minutes per day to four hours per day resulting in total, therapist delivered doses of eight hours to 30 hours. Three of the studies included a home program and specified total doses ranging from 16.2 to 36.8 hours (Hoare 2013; Sakzewski 2015a; Wallen 2011).

Dose-matched comparison groups

Fifteen studies employed a high-dose comparison intervention. The majority of these were described as either Hand Arm Bimanual Intensive Training (HABIT) (Gelkop 2015; Gordon 2011) or bimanual interventions (Deppe 2013; Facchin 2011; Sakzewski 2011; Sakzewski 2015b; Zafer 2016), or conventional care delivered by occupational therapists and/or physiotherapists (Aarts 2010; Abd El-Kafy 2014; Smania 2009; Sung 2005; Xu 2012). One study each used "intensive motor therapy" (Kirton 2016a (CIMT + r TMS); Kirton 2016b (CIMT + sham TMS)), virtual reality (Rostami 2012b) or "Remind to Move" (a wrist-worn sensory cueing device to alert children to do customised movement tasks with the affected upper extremity) (Dong 2017).

The average total dose, including therapist delivered and home program hours for the 15 dose-matched interventions was 71.4 hours (range six to 210 hours). This is lower than the dose we report for the dose-matched CIMT interventions (129 hours) as the forced use component integral to several of the CIMT studies (for example, those using casting for 24 hours per day as a means of constraint) was factored into the average dose. Dose-matched comparison interventions were carried out by therapists over one to 10 weeks, from one day per fortnight to six days per week, in sessions of 30 minutes per day to eight hours per day resulting in total doses of therapist guided intervention of two hours to 120 hours. Seven of nine studies which specified using a home program as part of the intervention reported total doses of home programs ranging from 10 to 120 hours.

Different form of CIMT comparison groups

Three studies employed a different form of CIMT as the comparison intervention. DeLuca 2012 used a high-dose hCIMT intervention delivered three hours per day instead of six hours per day - the form was otherwise identical. Rostami 2012a compared clinic-based CIMT with home-based CIMT delivered by an occupational therapist. More recently, Christmas 2018 compared prolonged constraint using a custom-made semi-rigid cast with intermittent hand holding.

The average total dose, including therapist-delivered, forced use (restraint worn most of the waking day) and home program hours across the three studies which used a different form of CIMT as a comparison intervention was 91 hours (range 42 to 168 hours). In two of the studies, interventions were carried out with therapists, over two to three weeks, from five to seven days per week, in sessions of 90 minutes per day to three hours per day resulting in total doses of 15 to 63 therapist-delivered hours. One study specified that no home program was included (DeLuca 2012) and the other study reported 101 hours of home program (Rostami 2012a). In the third study (Christmas 2018), hand holding was used as a form of restraint by families in usual settings for 42 hours, one hour per day, over three blocks of two weeks during in a 10-week period.

Outcomes

We have summarised the included outcomes in Table 6. Excluded outcomes and reasons for exclusion are provided in Table 3.

A total of 57 outcome measures were used across all included trials. Thirty (52%) of these measures were only used in a single trial. The mean number of outcomes used in each trial was four (range one to 14). The most commonly used measure was the Assisting Hand Assessment (AHA), which was used in 15 trials (Aarts 2010; Al-Oraibi 2011; Christmas 2018; DeLuca 2012; Deppe 2013; Eliasson 2011; Eliasson 2018; Gelkop 2015; Gordon 2011; Hoare 2013; Kirton 2016a (CIMT + r TMS); Sakzewski 2011; Sakzewski 2015a; Sakzewski 2015b; Wallen 2011). We did not include data from five studies in any of the analyses for a combination of reasons: none of the included outcome measures possessed adequate reported validity or reliability (or both) for children with CP; standardised assessments were invalidated because the administration or scoring was adapted; and/or the data were not reported or made available (Abd El-Kafy 2014; Hosseini 2010; Rostami 2012a; Rostami 2012b; Smania 2009).

Funding sources

Five studies failed to report on funding (Abd El-Kafy 2014; Choudhary 2013; Gelkop 2015; Smania 2009; Yu 2012); two studies reported receiving no funding (Deppe 2013; Zafer 2016); for three studies we did not have a translation available to assess funding (Abootalebi 2010; Gharib 2010; Sabour 2012); 13 studies reported being funded by research councils (de Brito Brandão 2010 ; Charles 2006; Chen 2014; Christmas 2018; Eliasson 2011; Eliasson 2018; Gordon 2011; Sakzewski 2011; Sakzewski 2015a; Sakzewski 2015b; Taub 2004; Taub 2011; Wallen 2011); eleven studies reported being funded by the host institution (Al-Oraibi 2011; de Brito Brandão