Department of Health and Care Sciences

Effectiveness of constraint-induced movement therapy compared with bimanual intensive training in children with spastic unilateral cerebral palsy - a systematic review

Maria Tervahauta

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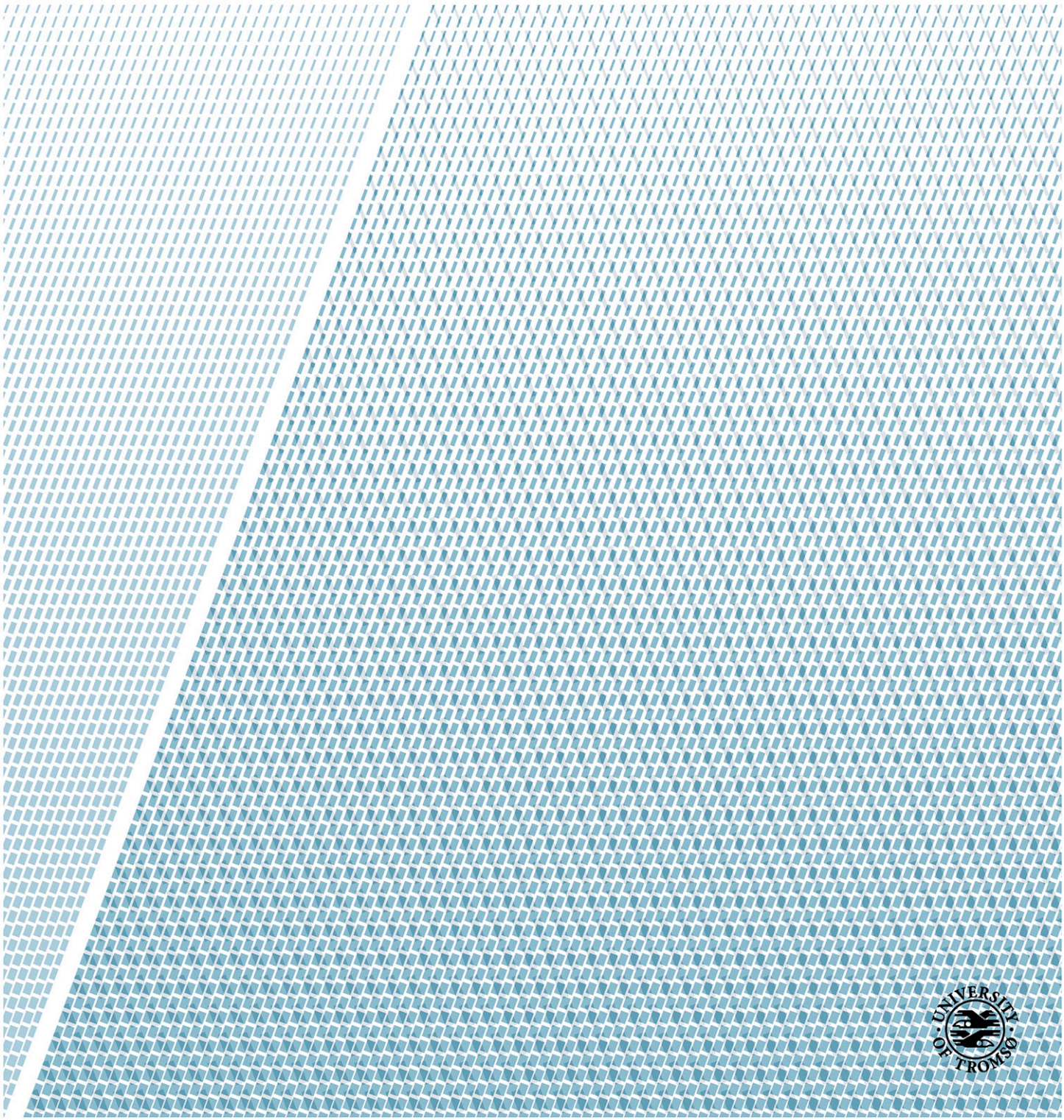

“The wonder of being lies in aliveness and the wonder of aliveness originates in movement.”

\- Maxine Sheets-Johnstone, 1999

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Abstract

AIM The aim of this study was to systematically assess the effectiveness of Constraint-Induced Movement Therapy (CIMT) compared with Bimanual Intensive Training (BIT) across the domains of the International Classification of Functioning, Disability and Health - Children and Youth (ICF-CY) in children with spastic unilateral cerebral palsy (CP).

METHOD A systematic literature review using the American Academy for Cerebral Palsy and Developmental Medicine (AACPDM) methodology was conducted. The following databases were searched: CINAHL, Cochrane Library, EMBASE, MEDLINE, PEDro, Pubmed and PsycINFO. The primary outcomes of interest were bimanual upper extremity (UE) function, unimanual UE function and participation. The secondary outcomes of interest were individualised goals and quality of life. The quality of conduct of the included trials was rated by two independent reviewers using the AACPDM rating questions. The standardised mean difference (SMD) and 95% confidence intervals (95%CI) were calculated using post-scores.

RESULTS Six RCTs met the inclusion criteria, one with high, three with moderate and two with low quality of conduct. The dose of the intervention varied from a total of 60 hours over 10 days to 210 hours over 10 weeks. Follow-up varied from immediate post-intervention to 52 weeks. No adverse events were reported. The measurement instruments used assessed items across the ICF-CY domains making it not possible to comprehensively report the findings using the ICF-CY. In general, no or minimal differences in the effectiveness of CIMT compared with BIT were observed in the outcomes of interest at any follow-up. The 95%CIs were consistently wide. The mean group pre-post change scores exceeded a known minimal detectible change (MDC) in both groups only when attainment of individualised scores was measured with the COPM. It was not possible to calculate SMD for the quality of life outcomes. A meta-analysis was assessed to be little relevant due to high variability in dosing, the used measurement instruments and the variability in the children's response.

INTERPRETATION Based on the findings in the RCTs included in this systematic review, it is not possible to confidently say that CIMT or BIT is more effective than the other in improving manual ability, participation and individual goals in children with unilateral CP at group-level.

KEYWORDS unilateral cerebral palsy, constraint-induced movement therapy, bimanual intensive training, upper extremity function, ICF

Sammendrag

FORMÅL Formålet med denne studien var å utforske effekten av Constraint-Induced Movement Therapy (CIMT) sammenlignet med Bimanual Intensiv Trening (BIT) på tvers av kategoriene i den Internasjonale Klassifikasjonen av Funksjon, Funksjonshemming og Helse – for barn og ungdom (ICF-CY) hos barn med unilateral cerebral parese (CP).

METODE En systematisk litteraturgjennomgang ble gjennomført ved bruk av American Academy for Cerebral Palsy and Developmental Medicine (AACPDM) metodologi. Det ble søkt i følgende databaser: CINAHL, Cochrane Library, EMBASE, MEDLINE, PEDro, Pubmed og PsycINFO. Effekt av intervensjonene på bimanuell hånd- og armfunksjon, unimanuell hånd- og armfunksjon og deltagelse var av størst interesse. Individuelle mål og livskvalitet var av sekundær interesse. Kvaliteten på de inkluderte studiene ble vurdert av to uavhengige personer ved bruk av AACPDM 'quality of conduct' spørsmål. Standardised mean difference (SMD) og 95% konfidensintervall (95%CI) ble beregnet av post-skårer.

RESULTATER Seks RCT-studier ble inkludert, én med høy, tre med moderat og to med lav kvalitet. Intervensjonsmengden varierte fra 60 timer fordelt på 10 dager til 210 timer fordelt på 10 uker. Oppfølgingsperioden varierte fra umiddelbart etter avsluttet intervensjon opp til 52 uker etter. Det ble ikke rapportert om negative bivirkninger. Målingsinstrumentene som ble benyttet vurderte elementer på tvers av kategoriene i ICF-CY, noe som gjorde det umulig å rapportere resultatene i tilknytting til de spesifikke ICF-CY kategoriene. Generelt, ingen eller minimal forskjell mellom CIMT sammenlignet med BIT ble observert. 95% kondifensintervall av SMD var konstant brede. Gjennomsnittlig pre-post endring i begge gruppene overskred minste målbare endring kun når individuelle mål ble vurdert med COPM. Det var ikke mulig å beregne SMD for instrumentene som målte livskvalitet. En meta-analyse ble vurdert til å være av lite relevans på grunn av store variasjoner i intervensjonsmengden, målingsinstrumentene som ble brukt og barnas respons til intervensjonene.

FORTOLKNING Basert på resultater fra RCTer som ble funnet i denne systematiske litteraturgjennomgangen, er det ikke mulig å si at CIMT eller BIT har bedre effekt enn den andre for å bedre hånd- og armfunksjon, deltagelse og oppnåelse av individuelle mål hos barn med unilateral CP på gruppenivå.

NØKKELORD unilateral cerebral palsy, constraint-induced movement therapy, bimanual intensive training, upper extremity function, ICF

Preface

This thesis was prepared in accordance with the guidelines for Master thesis by UiT - the Arctic University of Norway. Based on the guidelines the thesis is an individual piece of scientific work of a self-chosen theme up to 25 000 words (excluding the front page, acknowledgements, table of contents, bibliography and supplementary material). In line with the UiT guidelines, all references follow the APA format.

The chapters of this thesis are organised as follows:

Chapter 1 provides an overview of the topic with a general introduction.
Chapter 2 provides the theoretical background upon which the thesis is build.
Chapter 3 explains the methods used.
Chapter 4 presents the results.
Chapter 5 provides a discussion of the findings.
Chapter 6 provides a short conclusion for the findings.

The following supplementary material is provided:

I. Search strategy for each database
II. References for qualitative studies
III. List of publications from the research groups
IV. Reasoning for quality of conduct scoring

All references are compiled in a bibliography at the end of the thesis.

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Abbreviations

AACPDM American Academy of Cerebral Palsy and Developmental Medicine

AHA Assisting Hand Assessment

Assessment of Life Habits for Children

BIT Bimanual Intensive Training

CI confidence interval

CIMT Constrained-Induced Movement Therapy

CNS Central Nervous System

CEBM Centre for Evidence Based Medicine

CP Cerebral Palsy

COPM Canadian Occupational Performance Measure

EBM Evidence-Based Medicine

EBP Evidence-Based Practice

GMFCS E&R Gross Motor Function Classification Scale Extended and Revised

ICF International Classification of Functioning, Disability and Health

ICF-CY Classification of Functioning, Disability and Health - Children and Youth

The Jebsen–Taylor Test of Hand Function

MACS Manual Ability Classification System

MCID Minimal clinically important difference

MUUL Melbourne Assessment of Unilateral Upper Limb function

PEDI Pediatric Evaluation of Disability Inventory

PRISMA Preferred Reporting Items for Systematic reviews and Meta-Analyses statement

QoL Quality of life

QUEST Quality of Upper Extremity Skills Test

RCT Randomised controlled trial

SCPE Surveillance of Cerebral Palsy in Europe

SD Standard deviation

SDC smallest detectable change

SMD Standardised mean difference

UE Upper extremity

WHO World Health Organization

WCPT World Confederation of Physical Therapy

1. Introduction

Moving, touching and manipulating objects is fundamental to our ability to participate in and learn about the world (Sheets-Johnstone, 1999, pp. 226-229). We engage in daily activities, occupations and social contact with the aim to do something useful for ourselves and for others. The full meaning of manual competency, therefore, is created in the context of our relationships with others. Furthermore, doing something useful is the key to building, shaping and expressing identity. Developing identity though daily activities and occupations thus creates the context for a meaningful life, and as Christiansen (1999, p. 547) discusses further, life meaning helps us to be well.

Most children with spastic unilateral cerebral palsy (CP) have the intellectual capacity to attend regular schools, and essentially the same societal demands and expectations are placed on these children as on non-disabled children (Sakzewski, Ziviani, & Boyd, 2009, p. e1111; Skold, Josephsson, & Eliasson, 2004, p. 416). Whereas the majority of the children with unilateral CP achieve independent walking, impaired upper extremity (UE) function contributes to about half of the children experiencing limitations in activities of daily living and restrictions in participation in education, leisure and occupational activities (Fedrizzi, Pagliano, Andreucci, & Oleari, 2003, p. 85; Gordon, 2010, p. 315; Pagliano et al., 2001; Sakzewski et al., 2009, p. e1111).

Because of the non-progressive disturbances in the foetal or the developing infant brain, children with unilateral CP experience intrinsic limitations in their manual ability, such as impairments in muscle tone, strength, sensation, motor planning and control as well as coordination of UE movements (Gordon, 2011, p.57; Sakzewski et al., 2009, p. e1111; Steenbergen, Verrel, & Gordon, 2007). Above unimanual tasks, these impairments typically contribute to limitations in activities where the use of the two hands is required (Facchin et al., 2009, p. 217; Gordon, 2010, p. 315; Steenbergen, Charles, & Gordon, 2008).

Together with the impairments, behavioural aspects constitute an important factor affecting manual ability in children with unilateral CP. With a vast majority of activities in daily living,

education and occupations comprising of bimanual tasks, a mismatch between the children's capabilities and the task and societal demands may arise. In their interviews with children with unilateral CP, Skold et al. (2004, p. 423) describe that some children choose to omit difficult activities because they wish to conceal their disability and inability to complete activities akin to non-disabled children. As the children repeatedly experience difficulties in using the affected UE, many choose to find other solutions and/or adjust their behaviour to meet the task demands (Fedrizzi, Rosa-Rizzotto, Turconi, Pagliano, Fazzi, Pozza, Facchin, et al., 2013, p. 171; Houwink, Aarts, Geurts, & Steenbergen, 2011, p. 2158; Skold et al., 2004; Taub, Uswatte, Mark, & Morris, 2006). With constant negative reinforcement many children disregard the affected UE, even when the affected UE is only mildly impaired. This phenomenon is described as developmental disregard (Hoare, Wasiak, Imms, & Carey, 2007, p. 676; Houwink et al., 2011, p.2158), comparable to 'learned non-use' in adults after cerebrovascular accident (Taub et al., 2006; Taub, Uswatte, & Pidikiti, 1999, p. 239). Importantly, the lack of spontaneous use of the affected UE leads to asymmetrical development of the upper extremities, and may further contribute to secondary musculoskeletal impairments.

Throughout much of the 20th century motor impairments, especially in the UE, were thought to be static, with little potential for improvement (Gordon & Magill, 2012, p. 161). However, increasing evidence now demonstrate that manual ability is a dynamic phenomenon and may be changed by practice (Eliasson, 2007). Importantly, improvements in hand function have been observed to occur over a longer period of time than previously expected Eliasson et al. (2006, p. e1234). Based on the current motor learning theories, improving manual ability requires intensive training of targeted activities where children are provided with adequate opportunity, motivation, experience, and environment (Hoare et al. 2007; Sakzewski, Ziviani, & Boyd, 2014).

In the last decade, constraint-induced movement therapy (CIMT) and bimanual intensive training (BIT) have been proposed as suitable interventions. CIMT was developed from behavioural learning theories and discoveries in neuroscience, and is said to represent "a paradigm shift" in UE rehabilitation (Brady & Garcia, 2009). The focus is in reversing the behavioural aspects associated with the limited UE use by constraining, and thereby inducing,

increased use of the affected UE. Based on the fact that most daily activities are bimanual tasks, BIT was developed with the focus to improve the use of the affected UE as a support hand in functional bimanual activities (Charles & Gordon, 2006; Gordon, Schneider, Chinnan, & Charles, 2007). In line with the current motor learning theories, both interventions are based on intensive, repetitive, goal-oriented task practice where the children are incrementally provided with more challenging tasks.

Both CIMT and BIT have been reported to be more effective in improving UE function in children with unilateral CP than no treatment or very basic treatment (Hoare et al., 2007; Sakzewski et al., 2014). Although the results are promising, it remains unclear whether the efficacy of CIMT is due to the constraint or the intensive training (Gordon, 2011; Ferdizzi et al., 2013, p. 162; Sakzewski et al., 2009, p. e1118).

Recent primary research has therefore focused on comparing CIMT with BIT. To gather the results from randomised controlled trials (RCTs), Dong et al. (2013) conducted a systematic review with a narrative analysis. Although narrative analyses provide potentially valuable information, they do not allow for assessing the consistency of the intervention effects across the primary studies. Sakzewski et al. (2014) included RCTs comparing CIMT and BIT as part of their large meta-analysis. As the aim of the meta-analysis was to gathered data on all non-invasive UE interventions for children with unilateral CP, it did not include a comprehensive analysis of the RCTs comparing CIMT and BIT. To date, no systematic review has based its findings on the International Classification of Functioning, Disability and Health - Children and Youth (ICF-CY) (WHO, 2007). The ICF-CY provides an invaluable framework for standardised description of health and functioning, as well as a unified language for communication of research findings.

To fill the research gap, a systematic review was conducted with the aim to examine the effectiveness of constraint-induced movement therapy (CIMT) compared with bimanual intensive training (BIT) in children with spastic unilateral CP assessed on the different ICF-CY domains. The Guideline for Developing Systematic Reviews of Treatment Interventions for Children with Developmental Disabilities by the American Academy of Cerebral Palsy and Developmental Medicine (AACPDM) Treatment Outcome Committee (Darrah, Hickman,

O'Donnell, Vogtle, & Wiart, 2008) was used as the basis in this systematic review. The aim of the guideline is to produce systematic reviews with focus on using the ICF-CY as a framework and language for reporting findings in paediatric research.

Based on previous literature and theory of training specificity, it was hypothesised that CIMT and BIT show similar efficiency in improving UE function in children with unilateral CP, but that CIMT is more effective in improving unimanual UE function and BIT in improving bimanual UE function.

2. Theory

All observation is selectively orientated and no theory-free data exists, therefore, all research and interpretation of the evidence, is essentially directed by the researcher's though models (Thornquist, 2003, p. 197). This chapter provides an overview of the theoretical framework used in this thesis, as well as of other theory the work was build upon. The framework was build upon a variety of current theory in health care and rehabilitation sciences.

2.1. The International Classification of Functioning, Disability and Health

The International Classification of Functioning, Disability and Health (ICF) (WHO, 2001) provides the main conceptual framework and language for this thesis. The decision followed recommendations by the World Confederation of Physical Therapy (WCPT) that supported the implementation of the ICF in 2003 (Escorpizo et al., 2010, p. 1054). More specifically, the terminology of the version adapted for children and youth, the ICF-Children and Youth (ICF-CY), published by the WHO in 2007, was applied.

The ICF is build on the perspective that human functioning and disability consist of multidimensional, complex, and dynamic interactions between different domains of health that interact with environmental and personal factors (figure 1). Body functions comprise of physiological functions, e.g. cognitive functions, and body structures constitute of anatomical parts, e.g. organs or limbs. Activities entail execution of a task or action by an individual, and participation implies involvement in a life situation. Personal factors describe the background of an individual's life and living, and comprise of features of the individual that are not part of a health condition or health state. Environmental factors comprise of the physical, social and attitudinal environments in which people live. The contextual factors (personal and environmental factors) may either facilitate or be barriers to functioning (WHO, 2001; Rosenbaum & Stewart, 2004, p. 9). The domains are divided into chapters that are further organised into hierarchical categories which include increasingly detailed definitions on second, third, and sometimes fourth level.

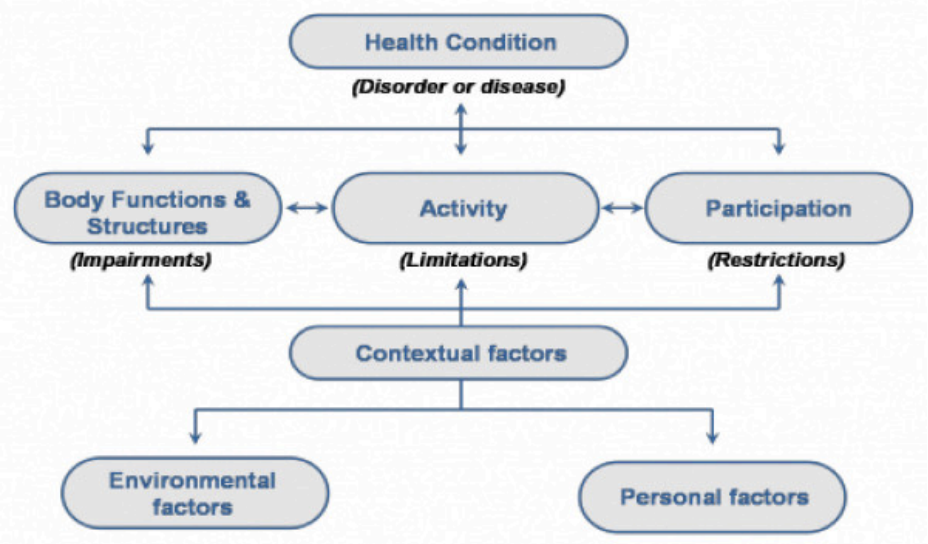

Figure 1. *The ICF-CY model displaying the interactions between the domains. Adapted from WHO (2007).*

The ICF emphasises the context in which functioning and disability occur. The concept of performance is used to describe what an individual does in his or her current, habitual environment, including the societal context. This includes involvement in life situations and the lived experience of the person in the context of his or her actual environment. In contrast, the concept of capacity describes the person's ability to function in a standardised environment (WHO, 2001, p. 11). Knowledge about the person's capacity and his or her performance enables determination of any gaps between the person's best abilities and what he or she actually does in everyday life.

It is now well-recognised that a common language is essential in advancing the science of disablement, in communication between therapists and others working with the clients, and in the documentation of the health care processes (Jette, 2006, 2009; Rosenbaum & Stewart, 2004; WHO, 2001). A common language is essential for a uniform understanding of the results in primary studies as well as for assisting clinicians in the interpretation of the results in the context of other available resources. The ICF provides a framework for such a standard language (Wagner & Davids, 2012, pp. 1257-1258). However, for an efficient use of the ICF, it is essential that the users completely understand what the perspective of functioning of the ICF entails and what is does not entail. For instance, the ICF regards functioning as a distinct concept from quality of life and health preferences in the future. Functioning in the ICF perspective is related to the limitations and restrictions related to a health problem, where as

quality of life refers to how someone feels about these limitations and restrictions (Cieza et al., 2005, p. 212).

Over the last decades a range of, often competing, condition-specific and generic instruments have been developed to measure changes in functioning. With such a large selection of measurement instruments available, it has become increasingly difficult for researchers to select the most appropriate instruments for their trials, and for readers to interpret and compare the results of different trials (Cieza et al., 2005, p. 212). The "ICF linking rules" (Cieza et al., 2005) were therefore developed. The aim of the linking rules is to facilitate linking of outcome measures to the ICF domains. Importantly, as the measurement instruments used should reflect the aims of the interventions, the linking rules provide "a connecting framework between interventions and outcome measures, facilitating the selection of the most appropriate outcome measure for the aim of the intervention" (Cieza et al., 2005, p. 213).

2.2. Cerebral palsy

Definition

The definition of cerebral palsy (CP) was updated in 2005 to adjust to the advancements in the knowledge of physiological and pathological brain development, as well as to adapt to the changing concepts about impairments, functional status and participation brought upon by the ICF (Rosenbaum et al., 2007). Thus, in this thesis CP is recognised as *"a permanent disorder of movement and posture causing activity limitations attributed to non-progressive disturbances having occurred in the developing foetal or infant brain. The motor disorders of cerebral palsy are often accompanied by disturbances of sensation, perception, cognition, communication, and behaviour; by epilepsy; and by secondary musculoskeletal problems"* (Bax et al., 2005; Rosenbaum et al. 2007, p. 9).

Prevalence

CP is one of the most common causes of childhood physical disability (Oskoui, Coutinho, Dykeman, Jette, & Pringsheim, 2013, p. 509; SCPE, 2000, p. 816). A methodologically rigorous systematic review and meta-analysis based on population-based registries found an overall prevalence of 2.11 per 1000 live births (95% CI 1.98–2.25) (Oskoui et al., 2013, p. 511). A

population-based study in Norway found a prevalence of 2.1 per 1000 live births (Andersen et al., 2008, p. 6). Despite significant advances in pre- and perinatal care and falls in neonatal mortality generally, the prevalence of CP has remained stable over the past 40 years (Sigurdardottir, Thorkelsson, Halldorsdottir, Thorarensen, & Vik, 2009, p. 356).

Approximately 50% of the children with CP are born at term (Sigurdardottir et al., 2009, p. 357) with the prevalence of CP being highest among children born before 28 weeks of gestation (111.80 per 1000 live births; 95% CI 69.53–179.78), and lowest among children born after 36 weeks of gestation (1.35 per 1000 live births; 95% CI 1.15–1.59). In terms of birth weight, the prevalence is highest in children weighing 1000 to 1499g (59.18 per 1000 live births; 95% CI 43.38–73.95), and lowest in children weighing over 2500g (1.33 per 1000 live births; 95% CI 1.19–1.49) (Oskoui et al., 2013, p. 511).

Although the overall prevalence of CP has remained stable, changes in the characteristics of CP have occurred. The proportion of children with diplegia has increased, possibly reflecting increased survival of pre-term and very pre-term infants. The prevalence of children with quadriplegia has decreased, presumably due to advances in health care (Sigurdardottir et al., 2009, p. 356; Wright & Wallmann, 2012, p. 581). A population-based study in Norway studied the characteristics of CP in the Norwegian population and found that of all children with CP 33% (95% CI: 28–39) were classified with spastic unilateral CP, 49% (95% CI: 41–53) with spastic bilateral CP, 6% (95% CI: 4–10) with dyskinetic CP and 5% (95% CI: 3–8) with ataxic CP. The subtype could not be classified in 7% (95% CI: 4–11) of the children (Andersen et al., 2008, pp. 6-7). A similar prevalence of spastic unilateral CP has been reported in other countries (Hoare et al., 2007, p. 675; Sakzewski et al., 2009, p. e1111).

Etiology

The causes of CP are not completely understood. However, associations have been made to certain events arising prenatally in the foetus, perinatally at around birth, postnatally after birth or postneonatally more than 28 days after birth (Aarli, Andersen, Jansen, & Sommerfelt, 2010, p. 227; Wright & Wallmann, 2012, p. 578). Brain damage occurring after the child is two years old is classified as acquired brain injury (Aarli et al., 2010, p. 227). Some of the most important etiological factors include hypoxia or disturbance of circulation to the brain,

developmental disturbance in the brain without a genetic cause, infection or reaction to an infection, genetic causes, toxic causes (e.g. medication of the mother during pregnancy), and traumatic causes occurring during the first two years of life (Aarli et al., 2010, p. 227). The developmental stage of the brain at the time of the cerebral insult is decisive for the evolvement and prognosis of the characteristics of the child's cerebral palsy (Aarli et al., 2010, p. 227; Feys et al., 2010, p. 176).

Classification

The Surveillance of Cerebral Palsy in Europe (SCPE) (SCPE, 2000) classification of subtypes of CP, the Gross Motor Function Classification Scale Extended and Revised (GMFCS E&R) (Palisano, Rosenbaum, Bartlett, & Livingston, 2008) and the Manual Ability Classification Scale (MACS) (Eliasson, Forssberg, et al., 2006) were used as the main systems to communicate classification of children with CP in this thesis. Considering that gross motor function and manual ability do not fully correlate in children with CP (Carnahan, Arner, & Hagglund, 2007), together the classification systems provide a complementary communication system for the clinic and for research and administration purposes (Rosenbaum, Palisano, Bartlett, Galuppi, & Russell, 2008, p. 249).

The Surveillance of Cerebral Palsy in Europe (SCPE). The SCPE classification system on subtypes of CP was developed by a European-wide collaboration group in 2000 (SCPE, 2000). The four subtypes of CP are defined as follows (Cans et al., 2007, pp. 36-37):

- Spastic CP is characterised by increased tone and pathological reflexes, observed as increased reflexes, e.g. hyperreflexia, or pyramidal signs, e.g. positive Babinski. Depending on the involvement of the limbs, the terms spastic unilateral or bilateral CP are used.
- Ataxic CP is characterised by loss of orderly muscular coordination so that movements are performed with abnormal force, rhythm and accuracy.
- Dyskinetic CP is characterised by involuntary, uncontrolled, recurring, and occasionally stereotyped movements. The primitive reflex patterns predominate and the muscle tone is varying. Dyskinetic CP is further divided into dystonic CP dominated by abnormal postures and hypertonia, and choreo-athetotic CP dominated by hyperkinesia and hypotonia.

The Gross Motor Function Classification Scale Extended and Revised (GMFCS E&R). The GMFCS E&R is a valid, reliable and clinically meaningful system to classify gross motor function in children with CP aged 2 to 18 years (Palisano et al., 2008; Rosenbaum et al., 2008, p. 250). Focus is on the child's usual performance in sitting, walking and wheeled mobility and on self-initiated movement. The system is divided into five levels with each level being described specifically for four different age groups to account for the fact that although CP is a non-progressive condition, motor function changes over time (Rosenbaum et al., 2008, p. 250). A full description of the GMFCS E&R is available from www.canchild.ca. The general headings for the GMFCS levels are described as follows:

- Level I: the child walks without limitations.
- Level II: the child walks with limitations.
- Level III: the child walks with a hand-held mobility device.
- Level IV: the child has limited ability for independent mobility, and may require an electrical wheelchair.
- Level V: the child has limited ability to maintain antigravity head and trunk postures, and are transported in manual wheelchair in all settings.

The Manual Ability Classification Scale (MACS). The MACS is a valid, reliable and clinically meaningful system used to classify manual ability in children with CP aged 4 to 18 years of age. The focus is on assessing the child's self-initiated ability to handle objects in daily activities, and the need for assistance or adaptation in performing bimanual manual activities in everyday life (Eliasson, Krumlinde-Sundholm, et al. 2006; Ohrvall, Krumlinde-Sundholm, & Eliasson, 2013). The function of the two hands is not separated but considered together. The MACS is limited to situations where objects are manipulated within the reach of the child, this to ensure minimal influence of gross motor function on the classification of fine motor skills (Eliasson et al., 2006, p. 553). A complete description of the MACS is available from www.macs.nu. The MACS levels are generally described as follows:

- Level I: the child handles objects easily and successfully.
- Level II: the child handles most objects but with somewhat reduced quality and/or speed.
- Level III: the child handles objects with difficulty, and needs assistance to prepare and/or modify activities.

- Level IV: the child handles a limited selection of easily managed objects in adapted situations.
- Level V: the child does not handle objects and has severely limited ability to perform even simple actions.

Other classification systems. In addition to the MACS, other systems have been used to classify UE function in children with unilateral CP. The House classification (House, Gwathmey, & Fidler, 1981) is used to evaluate the function in the affected hand after surgery for thumb-in-palm deformity. The Zancolli classification (Zancolli & Zancolli, 1981) is used to grade the level of muscle tone in the wrist and finger flexors as well as active wrist and finger extension. These systems classify aspects of grasping instead of functional performance, and have not been tested for reliability (Eliasson, Krumlinde-Sundholm, et al., 2006, p. 549). A detailed description of the House and the Zancolli classifications is provided for example in Arner et al. (2008, p. 1340).

The classification systems & the ICF-CY

When considering these classification systems on the ICF-CY, it is clear that the SCPE classification is based on the body functions domain, while the GMFCS E&R and the MACS describe functioning primarily on the activities and participation domain. Both GMFCS E&R and MACS focus on assessing the child's performance in his or her habitual environment, distinct from the child's capacity (the best ability assessed in a standardised setting). Although the classification systems focus on activities and participation, some of the concepts used to distinguish between the GMFCS and MACS levels belong to the ICF-CY body functions or environmental factors domain. For instance, the distinction between GMFCS levels II, III and IV in children aged 6 to 12 years is based on the child's need for mobility devices, a concept belonging to the environmental factors domain. The distinction between the MACS and GMFCS levels I and II in children aged 6 to 12 years is based on the quality of movement including concepts such as speed, balance and coordination. Of these, coordination and balance belong to the body functions domain (b755 Involuntary movement reaction functions, b760 Control of voluntary movement functions, b765 Involuntary movement functions). Speed of movement is not currently classified on the ICF.

2.3. Manual ability

Adapting the conceptual framework employed by Eliasson et al. (2006) in the MACS, the definition of manual ability by Penta et al. (2001) is used in this thesis. Penta et al. (2001, p. 1627) defined manual ability as "the ability to manage daily activities that require the use of the upper limbs, whatever the strategies involved". The quality and extend of manual ability depends on a complex interplay between several factors within the individual, the task and the environment (Shumway-Cook & Woollacott, 2012, pp. 477-478). Because manual ability comprises a behaviour, it should be observed, and assessed, as a person's performance of activities in his or her everyday context (Eliasson et al., 2006, p. 549; Penta et al., 2001, p. 1627).

Knowledge of the development of manual ability is imperative for understanding the possibilities and possible effects of UE interventions. While genetics provide the child with a general blueprint for neural development, the development of the unique neural patterns in the brain is largely driven by experience and environmental requirements (Galea, 2014, p. 71). The brain is a dynamic, self-organising system that spontaneously adapts and changes to the requirements it is presented with in pre- and postnatal life (Braun & Bock, 2011, pp. 14-15).

All development is mediated by ongoing, bi-directional interchange between hereditary factors and the environment (Braun & Bock, 2011, p. 14). Edelman's theory of neuronal group selection (Edelman, 1989) highlights the interaction between nature and nurture in the development of any skills. First, the 'primary repertoires' of neuronal groups are developed as epigenetic factors regulate the structural diversity of the neural groups via cell division, cell differentiation, programmed cell death and neuronal migration. Second, in the post-natal life the strength of the developed synaptic connections in the neuronal groups are modified based on the requirements they are predisposed to, forming the 'secondary repertoires' of neuronal groups. Third, interconnected series of neuronal groups develop dynamic neural "maps" that independently receive inputs from the real world.

Development of fine motor skills in typically developing children is characterised by rapid progression during the first years of life followed by refinement of skills throughout the childhood (Eliasson, Forssberg, et al., 2006, p. e1227; Holmefur, Krumlinde-Sundholm,

Bergstrom, & Eliasson, 2010, p. 352). Some elements of manual ability, particularly locating objects in space and transport of the arm, may be present at rudimentary form at birth with other movement components, such as grasp, develop during the first year of life (Shumway-Cook & Woollacott, 2012, p. 505). As described by Boyd et al. (2014) UE skills in general develop in several non-consecutive stages including 1) discovering the hand; 2) visually regarding the hand; 3) visually exploring objects in space; 4) swiping at objects; 5) contacting objects; 6) ineffectively grasping objects; and 7) developing prehensile movements to better grasp objects.

Relatively little is known about the specific development of manual ability in children with unilateral CP (Eliasson, Forssberg, et al., 2006, p. e1227), and few tools exist for prediction purposes (Holmefur et al., 2013, p. 72). Holmefur et al. (2010) performed a longitudinal study in which they observed that children who used the affected UE for grasping at 18 months of age, had a more rapid development and reached a higher level of manual ability than children who did not use their affected hand. Children who had a higher manual ability reached 90% of their ability limit at 3 years of age, whereas children who had a lower manual ability developed more slowly, reaching 90% of their ability limit at 7 years of age. Importantly, it has been observed that improvements in manual ability continue even after adolescence regardless of the initial severity of the child's hand function (Eliasson, Forssberg, et al., 2006, p. e1232). The subsequent decline or improvement of skills after this time may be dependent on both severity of impairment and access to ongoing intervention (Eliasson, Forssberg, et al., 2006, p. e1234; Fedrizzi, Pagliano, Andreucci, & Oleari, 2003, p. 91).

A longitudinal study compared data from neuroimaging with the children's scores on the Assisting Hand Assessment (AHA) and found associations between the type, location and size of the perinatal brain lesion and the development of manual ability (Holmefur et al., 2013, p. 76). Children with white-matter lesions tend to obtain higher manual ability limits than children with middle cerebral artery (MCA) lesions (Feys et al., 2010; Holmefur et al., 2013, p. 76; Holmstrom et al., 2010). However, independent of the type of the brain lesion, the strongest predictor for development of better manual ability was the absence of combined involvement of the basal ganglia and the thalamus (Feys et al., 2010; Holmefur et al., 2013, pp. 75-76).

Considering that the thalamus is central for providing the cerebral cortex with the key information of representations of body space and extra-personal space, both of which essential for all complex behaviour (Galea, 2014, p. 73), this structural impairment corresponds with the finding that children with unilateral CP commonly present with deficits in movement planning (Steenbergen & Gordon, 2006, p. 780). As Steenbergen & Gordon (2006, p. 781) describe, movement planning involves anticipation of the future state of the motor system, and the consequences of an action, and is an essential for any function because of the inherent delays in the sensorimotor system. With bimanual tasks being generally more complex than unimanual tasks and requiring higher levels of motor planning, it is not surprising that children with unilateral CP typically have limitations especially in activities where the use of the two hands is required (Gordon, 2010, p. 315; Facchin et al., 2009, p. 217; Steenbergen et al., 2008).

Experience of actions is essential for development of internal models used to anticipate the consequences of those actions. Even though many children with unilateral CP present with a mild impairment of the more affected UE, many choose not to use the UE to its full potential in daily life, a phenomenon described as developmental disregard (Hoare et al., 2007, p. 676; Houwink et al., 2011, p. 2158). With the missing experience of actions, deficits in the development of internal models may add to further impairments in motor planning and manual ability. Importantly, research has shown that children with unilateral CP may have the capacity to improve their manual ability with sufficient practice. For example, in a study by Duff & Gordon (2003) a group of children with unilateral CP were not initially able to appropriately plan their fingertip forces on their affected UE to pick up different objects, yet they were able to do so with sufficient practice.

2.4. Assessing manual ability

The complexity of manual ability together with the heterogeneous population of children with unilateral CP makes assessment of manual ability a challenge (Vargus-Adams, 2009). A wide range of instruments are available to measure different aspects of manual ability and function in this population, yet the constructs and psychometric properties of these

instruments vary widely. A range of measurement instruments are presented in the methods section in this thesis and recent systematic reviews provide additional information, see for example James et al. (2013), Lemmens (2012), Carlon et al. (2010), Gilmore et al. (2010), Klingels et al. (2010), Baird et al. (2010), Davis et al. (2010), Harvey et al. (2008), and Sakzewski et al. (2007).

To obtain accurate information, the measurement instruments must be valid in that they measure what they are meant to measure, and reliable in that it can be ensured that the measurements are stable in time and between different persons completing the measurements. The instruments should be easily and readily employable and be sensitive to detecting change in function. The smallest detectable change (SDC) is an estimate of the smallest amount of change that can be considered a real change in function, and not a measurement error. The minimal clinically important difference (MCID) defines a threshold "that says when a person/group has just begun to experience what is an important improvement" (Beaton, Boers, & Wells, 2002, p. 109; Vargus-Adams, 2009, p. 7).

2.5. Evidence-based practice

In the past 20 years evidence-based practice (EBP) has become an essential ingredient of all health care practice (Dijkers, Murphy, & Krellman, 2012), and the evolving paradigm is the driving force of many physiotherapy vision statements, for instance in the American Physical Therapy Association's (APTA) Vision 2020 (APTA, 2014). The international description of physical therapy, as part of the policy statement of the World Confederation for Physical Therapy (WCPT), advocates that all member organisations' definition of physiotherapy must emphasise the need for practice to be evidence-based whenever possible (WCPT, 2013). In their much-cited definition, the original Evidence-based Medicine Working group at McMaster University in Canada defined evidence-based medicine as

"the conscientious, explicit, and judicious use of current best evidence in making decisions about the care and individual patients. The practice of evidence based medicine means integrating individual clinical expertise with the best available external clinical evidence from systematic research" (Sackett, Rosenberg, Gray, Haynes, & Richardson, 1996, p. 71).

Different professions have adjusted the definition during the years, yet all definitions are variations of the original. Importantly, most rehabilitation professions have integrated language concerning patient values in their definitions of EBP (Dijkers et al., 2012, p. S165). In the original article, Sackett et al. (1996, p. 72) write

> *"...without clinical expertise, practice risks becoming tyrannised by evidence, for even excellent external evidence may be inapplicable to or inappropriate for an individual patient".*

Thus, to ensure full appreciation of the concept of EBP, it is essential to emphasise that EBP implies integration of findings attainted through systematic research, knowledge attained through professional practice and expertise, and the values of the individual patient (figure 2). Using his or her clinical reasoning skills and clinical expertise to consider these three aspects, the physiotherapist considers, and re-considers, whether the findings from research may be applicable for the individual patient (Howick et al., 2011; Jewell, 2011, pp. 26-29).

Figure 2. *Components of evidence-based practice.*

As Dijkers et al. (2012, p. S166) point out, statements of what constitute 'evidence' differ depending of the time, place and culture. Traditionally, the model of "best evidence" has been fixed, and a categorical interpretation of evidence, in that studies using a certain type of research method give a claim more evidential support, has been a driving force in EBP (Kerry, Eriksen, Lie, Mumford, & Anjum, 2012, p. 1007). However, with EBP having expanded from simple pharmaceutic treatments to areas of health care dealing with complex interventions, it is well-recognised that different types of methods are needed to produce evidence for different types of clinical questions (Dijkers et al., 2012, p. S168; Hart & Bagiella, 2012). As emphasised in the ICF framework, human functioning consists of complex, dynamic relationships between biopsychosocial aspects. No one research method is applicable to study all these relationships. Different methods are required to answer clinical questions

concerning the “measurable” aspects of phenomena relevant for practice, for instance the effect of an intervention, and the “meaning” of these phenomena, for instance the meaning children and their families attach to improving manual ability. A high-quality study, be it quantitative or qualitative, provides high level evidence when its findings are based on robust methodology that minimises bias (Howick et al., 2011). This is reflected in the revised evidence hierarchies developed by the Centre for Evidence Based Medicine (CEBM) by the University of Oxford (Howick et al., 2011).

2.6. The randomised controlled trial

Traditionally, the randomised control trial (RCT) has been referred to as “the gold standard” method, and it has subsequently been placed on top of the evidence hierarchy for quantitive research. The RCT has gained this position because of its inherent desire to minimise bias through randomisation and strive for standardisation of the variables of interest. The RCT is useful for testing an intervention in a rigorous way at group-level; as a result, it provides the mean effect for the group and how much variation or dispersion from the average exists (the standard deviation). RCTs are appropriate only in certain phases of the development and testing of interventions, at a point when there exists a need to demonstrate that a proposed new intervention has an effect of a size that is clinically meaningful in a certain patient group (Dijkers et al., 2012, p. S168; Whyte & Barrett, 2012). When the findings from the RCTs indicate a large variation in the patients’ response to the intervention, it would be important to further study for example which individuals respond best to the intervention, or to more closely study what is the particular mechanism of action of the intervention. Depending of the identified questions, a type of experimental design, where one of the independent variable is manipulated at a time, may provide with the best design to gain the needed evidence for applicability of the intervention for a specific population.

2.7. Systematic review & meta-analysis in EBP

With a huge growth in research publications (e.g. Sakzewski et al., 2014, p. e186), it is impossible for clinicians to keep up to date with the most current findings in primary research. Systematic reviews provide a means to gather and critically synthesise the findings

from primary research, and to understand the results of any single primary trial in the context of all other trials (Higgins & Green, 2011, p. 1.2.2.; Polit & Beck, 2012, p. 665; (Borenstein, Hedges, Higgins, & Rothstein, 2009, p. 9). Systematic reviews have several focus areas. On the one side, they explore the relationship between the independent variable (the variable that is manipulated, i.e. intervention) and the dependent variable (the variable that is affected by the independent variable, i.e. outcome). On the other side, important knowledge is gained from reviewing the methodological quality of the primary research, and the conclusions drawn from the studies (Higgins & Green, 2011, p.2.3.1; Cooper et al., 2009, pp. 5-6). Evaluation of the quality of conduct and risk of bias in the primary research enables assessment of the validity of the primary studies, i.e. the extent to which the design and conduct of the studies likely to prevent systematic errors (Higgins & Green, 2011, p. 79). The congregated findings give important indications for future research in the focus area.

A variety of measurement instruments based on different scoring systems are typically used in the primary studies, making it challenging for clinicians to draw conclusions about the meaningfulness of the outcomes for practice. Some systematic reviews are based on a narrative analyses of the findings in the primary research, and use the p-values to assess the important of the findings in the primary research. However, the p-value is only indicative of the strength of the evidence for that the null hypothesis is false (Polit & Beck, 2012, p. 477). The p-value can thus only indicate that the difference between the groups or the relationship between the variables is not zero, it does not give any indication about the size of the effect (Higgins & Green, 2011, p. 12). When some studies are statistically significant and others are not, the results are often interpreted as conflicting (Higgins & Green, 2011, p.12). The p-value is driven by a sample size, and therefore, as Higgins & Greene (2011, p.12) argue, reporting the p-value has no clinical importance, and basing practical conclusions on p-values is to miss the point of a review.

As an alternative, calculating effect sizes for the findings provides a way to convert the intervention outcomes measured with different instruments into a standardised value that describes the difference between the combined means of the intervention and the control groups divided by the means of the pooled standard deviation (Acton, 2001, p. 540). The effect size thus allows for comparison of the intervention effects on a standardised scale.

A common problem in research on children with CP is the small number of available participants (Kunz, Autti-Ramo, Anttila, Malmivaara, & Makela, 2006, p. 1239). Studies with small sample sizes are susceptible to random errors and overestimation of the real effect size (Acton, 2001, p. 540). A meta-analysis may therefore be useful in overcoming this problem as it allows for incorporation of the samples in the included primary trials into one large sample. Compared to primary studies with small sample sizes, meta-analyses are able to produce a more reliable and accurate conclusion of the direction, size, consistency and variance of the effect of the interventions across the primary studies (Polit & Beck, 2012, p. 654; Higgins & Green, 2011, p. 9; Field, 2009, p. 790). It provides a framework for evaluating the outcome data from a series of studies as a whole, rather than looking at each in isolation (Borenstein et al., 2009, p. xxiv). However, conducting a meta-analysis is not always appropriate. A common critique states that meta-analysis mixes apples and oranges (Dijkers, Murphy, et al., 2012, p. S170). However, as Polit & Beck (2012, p. 655) argue, meta-analysis should not be about "fruit", e.g. apples, but rather about a specific type of fruit, e.g. Granny Smith apples; a synthesis of various treatments offers little practical value (Acton, 2001, p. 542). When the heterogeneity of the primary studies is assessed to be significant, the method of choice is a systematic review with an in-depth narrative analysis of why the results are conflicting (Borenstein et al., 2009).

3. Methods

An explorative systematic review of randomised controlled trials (RCTs) was performed using the American Academy of Cerebral Palsy and Developmental Medicine (AACPDM) methodology (Darrah et al., 2008). The PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses statement) (Liberati et al., 2009) and the Cochrane Handbook for Systematic Reviews of Interventions (Higgins & Green, 2011) were used ensure quality of the review process.

Search strategy

A systematic, computer-aided literature search was performed in November 2013 and updated in April 2014. Following the AACPDM methodology, only original articles written in English and published in peer-reviewed scientific journals were included. The following databases were searched: Cumulative Index to Nursing and Allied Health Literature (CINAHL) Plus (up to week 18, 2014), the Cochrane Library (up to issue 5 of 12, May 2014), EMBASE (1980 to 2014 Week 18, 2014), Ovid MEDLINE (1946 to April Week 4, 2014), Physiotherapy Evidence Database (PEDro) (database updated 4 November 2013), PsycINFO (1806 to April Week 5, 2014), PubMed (up to week 18, 2014), The reference lists of the trials meeting the inclusion criteria were reviewed, and any missed relevant articles were added.

The search strategy was developed by MT and reviewed by Torstein Låg (PhD), the principle librarian at the Psychology and Law library at the University of Tromsø. The 'intervention' and the 'comparison' components of the search strategy were collapsed to increase the yield of possibly relevant for further manual examination. The strategy was adapted for other databases when necessary, and provided in supplementary material I. In Ovid MEDLINE the following search strategy was used:

1. Cerebral Palsy/
2. cerebral pals*.mp.
3. Hemiplegia/
4. hemipleg*.mp.
5. 1 OR 2 OR 3 OR 4
6. (constraint adj3 therap*).mp.
7. CIMT.mp.
8. CI therap*.mp.
9. unimanual.mp.
10. Restraint, Physical/
11. 6 OR 7 OR 8 OR 9 OR 10
12. HABIT.mp.
13. BIT.mp.
14. bimanual.mp.
15. 12 OR 13 OR 14
16. 5 AND (11 OR 15)

Criteria for considering studies for this review

The inclusion and exclusion criteria applied in this systematic review is specified in table 1 with additional reasoning provided below.

Types of studies

Due to limitations in the methodology of this review, qualitative studies were excluded. Nevertheless, following the AACPDM methodology, relevant qualitative studies were identified and the references provided (supplementary material II) as these studies supply relevant information and may be interesting for the reader.

Types of participants

Studies including children who had received Botox injections within six months prior to entering the trial were excluded. Although Botox injections alone have not been found to improve UE ability in children with unilateral CP, high-level evidence exists in that occupational therapy combined with Botox injections has a large effect in improving

Table 1. *Characteristics of the included and excluded trials.*

	Inclusion criteria	Exclusion criteria
Types of studies	- Studies using randomised controlled group research designs - Studies published in English in peer-reviewed scientific journals	- Systematic & non-systematic reviews - Expert opinions, case studies, conference abstracts - Qualitative studies - Unpublished studies
Types of participants	- Children with 'spastic unilateral CP (hemiplegia)' or 'congenital hemiplegia' aged 17 years and below	- Other subtypes of CP - Progressive conditions, spinal diseases, traumatic brain injury - Children who received Botox injections in the UE within 6 months prior to study entry - Children who had previously undergone CIMT or BIT
Types of interventions	- One group receiving CIMT and one group receiving BIT within the same trial - Any type of constraint used in the CIMT group - Interventions conducted in all environments	- Combinations of CIMT and BIT within one group (hybrid models) - CIMT or BIT amended with computer-based training / gaming
Types of outcome measures & measurement instruments	- Bimanual UE function* measured with: AHA, ABILHAND-Kids - Unimanual UE function* measured with: MUUL, QUEST - Participation in everyday activities*: PEDI, CAPE - Goal achievement**: COPM - Quality of life**: CP QOL-Child, CPCHILD	

Abbreviations: *AHA = Assisting Hand Assessment; MUUL = Melbourne Assessment of Unilateral Upper Limb function; QUEST = Quality of Upper Extremity Skills Test; CAPE = The Children's Assessment of Participation and Enjoyment; COPM = Canadian Occupational Performance Measure; GAS = Goal Attainment Scale; QoL = quality of life; * = primary outcome of interest; ** secondary outcome of interest.*

individualised outcomes, and a modest effect in improving quality of movement of the affected UE (Sakzewski et al., 2014, pp. e192-193) (B. J. Hoare et al., 2010, p. 2010). Studies including children who had previously undergone CIMT were excluded because children who participated in two courses of CIMT with 12 months between the interventions were found to maintain improvements from the first course of the intervention, and make further gains after the second course (Charles & Gordon, 2007).

Types of interventions

As the terms 'modified' CIMT and CIMT have been used inconsistently in paediatric literature, studies using either term were included. Only the term CIMT is used in this review. No restrictions in terms of the constraint used were applied as it has not been established that one type of constraint is more effective than another (Eliasson et al., 2013, p. 131). Interventions provided in all types of environment were included as it has not been established that one environment provides a more effective context for the interventions than another (Eliasson et al., 2013, p. 132).

Types of outcome measures

The primary outcomes of interest were bimanual UE function, unimanual UE function and participation in everyday activities. The secondary outcomes of interest were achievement of individual goals and quality of life. Potential measurement instruments with adequate psychometric properties were identified from recent systematic reviews. When the primary studies meeting the inclusion criteria employed measurement instruments that were initially overlooked, these instruments were further evaluated and included in the list of measurement instruments when they were assessed to have adequate psychometric properties. Existing literature was used to identify the ICF-CY domains assessed on each measurement. Reports based on the standardised ICF linking rules (Cieza et al., 2005) were preferred. The identified measurement instruments are described below with table 2 providing details of psychometric properties and the ICF domains of each instrument.

Assisting Hand Assessment (AHA). The AHA is a condition-specific instrument that assesses spontaneous use of the affected UE in bimanual activities (Hoare, Imms, Randall, & Carey, 2011; Krumlinde-Sundholm et al., 2007, p. 259). It is validated for children with unilateral CP or obstetric brachial plexus palsy aged 18 months to 12 years, and has excellent psychometric properties (Gilmore, Sakzewski, et al., 2010; Greaves, Imms, Dodd, & Krumlinde-Sundholm, 2010, p. 420; Klingels et al., 2010, pp. 892-895; Krumlinde-Sundholm, 2012, p. 808). The test development process is described in detail in Krumlinde-Sundholm et al. (2007) and Holmefur et al. (2007).

The AHA assesses six domains of bimanual ability including general use, arm use, grasp and release, fine motor adjustments, coordination and pace of performance. It is the only condition-specific UE instrument where most items assess concepts in the ICF-CY activity domain, or a combination of activity and body function [see Hoare et al. (2011, p. 993)] for a detailed analysis of the ICF-CY domains. The test is criterion-referenced with each item being scored on a four-point scale (1 = does not do; 2 = ineffective; 3 = somewhat effective; 4 = effective) (Krumlinde-Sundholm et al., 2007, pp. 259-260). The scores may be presented on a logic-scale or on a logic based 0-100 AHA-unit scale (Krumlinde-Sundholm, 2012).

Melbourne Assessment of Unilateral Upper Limb Function (MUUL). The MUUL is a condition-specific instrument that evaluates the quality of UE function in unimanual activities. It is validated for children with CP and other neurological impairments aged 18 months to 15 years, and has excellent psychometric properties (Gilmore, Sakzewski, et al., 2010, p. 20; Klingels et al., 2010, p. 895; Wagner & Davids, 2012). Four domains of upper extremity use are assessed including range of movement, accuracy (of reach and release), fluency of UE movement and dexterity (of grasp) (Hoare et al., 2011, p. 994). Hoare et al. (2011, pp. 990-991) provide a detailed description of the ICF-CY domains. The MUUL is criterion-referenced with each item being scored on a 3-, 4- or 5- point ordinal scale. The total test score is converted to a percentage score with a higher the percentage implying better UE function (Wagner & Davids, 2012, pp. 1267-1268).

Quality of Upper Extremity Skills Test (QUEST). The QUEST is a non-condition specific instrument based on neuro-developmental theories that evaluates the quality of UE function in unimanual activities. It is validated for children aged 18 months to 8 years with a neuromotor dysfunction involving spasticity, including but not limited to CP (Gilmore et al., 2010a, p. 16; Wagner & Davis, 2012; p. 1269). Although the QUEST presents with initial reliability, the administration, and scoring of some items remains unclear, and the reliability studies are based on only two raters (Gilmore et al., 2010a, p. 20).

The QUEST evaluates four domains including dissociated movements, grasp, protective extension, and weight bearing (Hoare et al., 2011, p. 992). Hoare et al. (2011, p. 992) provide a detailed description of the ICF-CY domains. The QUEST is criterion-referenced (Klingels et al.,

2012) with each movement and task being assessed as “yes” (2 points), “no” (1 point) or “not tested” (1 point) (DeMatteo, 1992, p. 14). Each UE is assessed and evaluated separately, and the total raw score is converted to a percentage score with a higher score representing better quality of UE movement (Wagner & Davids, 2012, p. 1269).

The Jebsen–Taylor Test of Hand Function (JTTHF). The JTTHF is a non-diagnosis specific instrument that evaluates unimanual hand use and movement efficiency in everyday activities (Sakzewski et al., 2011a, p. 666; Wagner & Davids, 2012, p. 1261). The test was originally developed and validated for the adult population and for typically developing children (Boyd et al., 2013, p. 12). Its validity and reliability in children with unilateral CP has not been established (Sakzewski et al., 2011a, p. 666). The JTTHF consists of a seven subtests including writing, flipping index cards, object placement, simulated eating, stacking checkers, and manipulating empty and full cans (Gordon et al., 2011, p. 694). A detailed analysis of the ICF-CY domains has not been conducted. The child is instructed to perform the tasks as rapidly and as accurately as possible, with the total score being the sum the times in each subtest (Islam et al., 2013, p. 4). A lower score indicates better function. The test has been modified for children with unilateral spastic CP in that the writing task has been removed and the time to complete each task was reduced to 2 minutes from 3 minutes to avoid frustration (Klingels et al., 2012, p. 892).

The Besta Scale. The Besta scale is condition-specific instrument consisting of three domains of UE function including grasp, bimanual use and activities of daily living that together compose a global score (Fedrizzi et al., 2013, p. 164). It has good interrater reliability (Fedrizzi et al., 2013, p. 164); other psychometric properties have been poorly evaluated or no information could be found. No analyses of the ICF-CY domains have been conducted. The items are assessed on four-point discrete, ordinal level scales. The quality of the grip is scored as follows: 0 = inability to grip cube; 1 = grasping or whole-hand grip; 2 = radial or three-finger grip; 3 = pincer grip. Spontaneous hand use and activities of daily living are scored based on the variability and stereotypy of movement patterns as follows: 0 = no use of impaired limb; 1 = use of impaired limb in a stereotyped pattern (wrist support); 2 = cooperation of the impaired hand in manipulation by holding with a restricted number of stereotyped patterns; 3 = cooperation of the impaired hand with holding and manipulation, using a varied repertoire of patterns (Facchin et al., 2009, p. 224).

Table 2. *Details of the measurement instruments.*

Measure	Purpose	Population	ICF-CY domains	Develop.	Validity	Respons.	Reliability	Administration
AHA	Spontaneous bimanual UE function	Children with unilateral CP or obstetric brachial plexus palsy aged 18mo – 12y (Krumlinde-Sundholm 2012)	- A or A-BF 78% - BF 23% (Hoare 2011)	Experts; Rasch-model (Gilmore 2010)	- Construct & content validity established; ++ - Construct validation with Rasch model (Klingels 2010, Gilmore 2010, Wagner 2012)	- SDD - raw scores: 3.89; logits 0.97 logits; logit based AHA-units (0-100): 5; - CMD: NA (Krumlinde-Sundholm 2012)	- Interrater: ICC 0.97-0.98; ++ - Intrarater: ICC 0.99; ++ - Test-retest: 0.98-0.99; ++ (Gilmore 2010, Klingels 2010, Wagner 2012)	- Therapist-led play session - Video recorded, scored later - Test 10-15min; 1h to score - Manual + stand. material - Certification process required (Gilmore 2010, Klingels 2010)
MUUL (revised)	Quality of unimanual UE function	Children with CP or other neurological impairment aged 30mo – 15y (Gilmore 2010)	- A 3% - A or A-BF 43% - BF 51% (Hoare 2011) - A & P 100% (Schiariti 2014)	Literature review; experts; Rasch-model (Hoare 2011)	- Construct + content validity established; ++ - Construct validation with Rasch model (Gilmore 2010, Klingels 2010, James 2013, Wagner 2012)	- SDD: 8.9% - CMD: NA (Gilmore 2010, Klingels 2010)	- Interrater: ICC 0.87-0.99; ++ - Intrarater: ICC 0.97-0.99; ++ - Test-retest: ICC 0.97-0.98; ++ (Gilmore 2010, Klingels 2010, Wagner 2012)	- Therapist-administered, standardised procedure - Video recorded, scored later - Test 30min; 30 min to score - Manual + standartised material required - Self-study, payment required (Gilmore 2010, Klingels 2010)
QUEST	Quality of unimanual UE function	Children with neuromotor dysfunction with spasticity (including but not limited to CP) aged 18mo – 8y (Wagner 2012)	- Dissociative movements: A - BF 21%; BF 79% - Weight-bearing: A-BF 8%; BF 92% - Protective extension: BF 100% - Grasp: A 7%; BF 93% (Hoare 2011)	NDT theory; literature review; clinicians & experts (Wagner 2012)	- Construct + content validity established; + (Gilmore 2010, Klingels 2010, Wagner 2012)	- SDD: 13.8% (Klingels 2010)	- Interrater: ICC 0.69-0.95; ++ - Intrarater: ICC 0.63-0.96; ++ - Test-retest: ICC 0.85-0.95; ++ (Gilmore 2010, Klingels 2010, Wagner 2012, Fedrizzi 2013)	- Therapist- administered - Direct observation or video recording - Non-standardised procedure - Test + scoring 30-45min - Free online manual - Self-study, no charge (Gilmore 2010, Klingels 2010,

Measure	Purpose	Population	ICF-CY domains	Develop.	Validity	Respons.	Reliability	Administration
JTTHF	Quality of unimanual UE function	Children with developmental disabilities 5-18y, non-diagnosis specific (Wagner 2012)	NA. (Scoring is based on speed of movement which currently is not classified on the ICF-CY.)	NA	NA on children with unilateral CP (Sakzewski 2011)	NA on children with unilateral CP (Sakzewski 2011)	NA on children with unilateral CP (Sakzewski 2011)	- Direct observation - 10-15min to complete - Payment required for manual & material (Klingels 2010)
Besta scale	Unimanual UE function, spontaneous bimanual UE function	Children with congenital hemiplegia (Facchin 2009)	NA	Analyses of clinical characteristic vs.etiologic factors (Fedrizzi 2003)	NA	NA	- Interrater: ICC 0.86; + (Fedrizzi 2013)	- Therapist-administered - Video recorded, scored later - NA on costs (Facchin 2009)
PEDI	Participation in everyday activities	Children with physical or with physical & cognitive disabilities aged 6 mo - 7.5y (James 2013)	Functional skills scale: - Self-care: concepts on A&P 113; BF 14; E 84 - Mobility: concepts on A&P 90; BF 3; E 102 - Social function: concepts on A&P 103; BF 17; E 44 (Ostensjo 2006)	Literature review; experts; normative/ clinical sample; Rasch-model (James 2013)	- Construct validity established; ++ - Validated with Rasch model (Østensjø 2006, James 2013)	- CMD: approx. 11 points (0–100 scale) (James 2013)	- Interrater: ICC 0.15–0.95 - Intrarater: NA - Test-retest ICC 0.67–1.0 (James 2013)	- Semi-structured parent interview - 30-60min to administer, 30min to score - Self-study - PEDI manual & scoring sheets (James 2013)
LIFE-H	Participation in everyday activities and social roles	Children with disabilities aged 5 - 13y (Sakzewski 2007)	- A & P (Adolfsson 2011, Sakzewski 2011)	Expert panel of parents, therapists, and researchers (Sakzewski 2007)	- Construct validity established; + (Sakzewski 2007)	NA	- Interrater: ICC 0.70–0.91 (except IR 0.62) - Intrarater: DA 0.82–0.96; SR >0.90 (except IR 0.62) - Test-retest: TS for SF 0.67 - Test-retest: TS for LF 0.73 (Sakzewski 2007)	- Self- or interviewer questionnaire - Administration time unclear - Access to manual unclear (Sakzewski 2007)

Measure	Purpose	Population	ICF-CY domains	Develop.	Validity	Respons.	Reliability	Administration
COPM	Occupational performance in self-care, productivity & leisure	All ages & disabilities (Sakzewski 2007)	- A & P 100% (Schiariti 2014)	Literature review; existing assessments; experts (Law 1990)	- Content validity established; + (Sakzewski 2007); ++ (Wagner 2012)	- CMD: 2 points; ++ (Cusick 2007, Sakzewski 2007)	- Interrater: NA - Intrarater: NA - Test-retest: 0.76-0.89; ++ (Sakzewski 2007, Wagner 2012)	- Semi-structured interview - 30-45min - Self-study - Payment required for some material (Wagner 2012)
CP-QOL Child	Quality of life	Children with CP aged 4 – 12 years (Wagner 2012)	- A 36.5% - BF 18.9% - E 29.7% - PF 5.4% (Schiariti 2011)	Grounded theory; consultation with cwCP and their parents (Carlon 2010)	- Construct, content and concurrent validity reported (moderate); ++ (Carlon 2010)	NA (Carlon 2010)	- Correlation between parent-proxy and child self-report data: ICC 0.52–0.77 - Test-retest: 0.76-0.89; + (Carlon 2010, Davis 2010, Wagner 2012)	- Parent-reported or child self-reported questionnaire - 15-25min to complete - Free of charge - Self-study, no charge (Carlon 2010, Wagner 2012)
KIDSCREEN -52	Quality of life	Children & adolescents aged 8-18y (Petersson 2013)	- A&P 20% - BF 46.7% - E 13.3% - P 6.7% - Undefinable: 13.3% (Schiariti 2014)	Literature; experts; focus groups; Rasch-model (Ravens-Sieberer 2008)	- Construct + content validity established; + (Ravens 2008, Davis 2010)	NA	- Test-retest: ICC 0.56-0.77 (Ravens-Sieberer 2008)	- Child self-report questionnaire / parent proxy questionnaire (Davis 2010)
3D kinematic measures	Kinematics & kinetics of movement	All	NA	Depends on the measure construct	Depends on the measure construct (Mercuri 2011)	Depends on the measure construct (Mercuri 2011)	Depends on the measure construct (Schneiberg 2010)	Depends on the measure construct
GAS	Individualised goal-setting	All ages & disabilities (Sakzewski 2007)	Depending on individual goal-setting	NA	- Variable results reported (Sakzewski 2007); ++ (Wagner 2012)	NA (Sakzewski 2007)	- Interrater: ICC 0.51-0.95; - Intrarater: ICC 0.96 - Test-retest: NA (Sakzewski 2007); + (Wagner 2012)	- Semi-structured interview - 60 min - Self-study, no payment (Sakzewski 2007)

Abbreviations: *A = activity; P = participation; A-BF = a combination of activity and body function / structure; E = environmental factors; PF = personal factors; + single study; ++ multiple studies; SDD = smallest detectible difference; CMD = clinically meaningful difference; NA = not available; CB = clinician based; PR = patient report; + single study; ++ multiple studies; TS = total score; DA = daily activities; SR = social roles; IR = interpersonal relationships.*

Pediatric Evaluation of Disability Inventory (PEDI). The PEDI is a non-condition specific semi-structured parent interview that evaluates the child's participation in everyday activities. The PEDI has been proposed to be the best measure to evaluate ADL capability in elementary school aged children (James et al., 2013, p. 9). It has strong psychometric properties, is responsive to meaningful clinical change, and has been found to be sensitive in detecting change after CIMT (James et al., 2013, p. 8). However, the dichotomous scoring scale may limit the test's ability to detect minor changes (James et al., 2013, p. 5). The PEDI has a broad item content and consists of three scales including functional skills items, caregiver assistance and environmental modifications. The functional skills scale is further divided in three domains including self-care functional skills, mobility and social functioning (James et al., 2013, p. 6). Ostensjo et al. (2006, p. 494) analysed the ICF-CY concepts. The self-care functional skills are rated on a nominal scale (0 = incapable; 1 = capable), the caregiver assistance items on a 6-point ordinal scale (0 = complete assistance, 5 = independence), and the environmental modifications as 'none', 'child-oriented', 'rehabilitation equipment' or 'extensive' (James et al., 2013, p. 6).

Assessment of Life Habits for Children (LIFE-H). LIFE-H is a non-condition specific questionnaire measuring participation in everyday activities and in social situations in home, school, and neighbourhood in children aged 5 to 13 years (Adolfsson, Malmqvist, Pless, & Granuld, 2011, p. 1236; Sakzewski et al. 2011b, p. 533). It has strong psychometric properties (Sakzewski et al. 2011b, p. 533), and covers the ICF activity and participation domains (Adolfsson et al., 2011; Sakzewski et al., 2007, p. 234). Two versions of the questionnaire exist, a long-form (197 items) and a short-form (64 items) (Sakzewski et al. 2011b, p. 533) . Each item is rated on a 10-point scale based on the level of accomplishment, type of assistance required, and the level of satisfaction. A score of 0 indicates total impairment (the activity or social role is not accomplished or achieved) and a score of 9 indicates optimal social participation (the activity or social role is performed without difficulty and without assistance) (Noreau et al., 2007, p. 667).

The Canadian Occupational Performance Measure (COPM). The COPM is a non-condition specific semi-structured interview evaluating self-perception of occupational performance in

self-care, productivity and leisure activities (Cusick, Lannin, & Lowe, 2007, p. 761; Sakzewski et al., 2007, pp. 237-238). The instrument was originally developed for the adult population (Law et al., 1990, p. 83), but can be used for people of all ages and disabilities. It has adequate psychometric properties (Sakzewski et al., 2007, p. 235). The user identifies activities he or she wishes improve. Three dimensions for each activity are evaluated, including the importance of the task, own capability to complete the task, and own satisfaction of the performance of the task. The items are scored on a 1-10 ordinal level scale (Wagner & Davids, 2012, p. 1265).

Cerebral Palsy Quality of Life - Child (CP QOL-Child). The CP QOL-Child is a condition-specific quality of life questionnaire designed to be used for children with CP aged 4 to 12 years (Waters et al., 2007, p. 49). Compared with other similar QoL instruments, it has strong psychometric properties (Schiariti, Fayed, Cieza, Klassen, & O'Donnell, 2011, p. 1338). It is based on a well-defined quality of life conceptual framework, making its conceptual properties strong compared to other QoL instruments (Davis et al., 2010; Schiariti et al., 2011, p. 1338). The questionnaire is available in two versions including a self-report version for children aged 9 to 12 years, and a parent proxy report for children aged 4 to 12 years. Five domains of quality of life, including social well-being, emotional well-being, participation, function, pain and impact of disability are rated on a 9-point, ordinal level scale (Carlon et al., 2010, p. 6; Wagner & Davids, 2012, p. 1265). The parent proxy report additionally assesses access to services and the family's health (Waters et al., 2007). A detailed analysis of the ICF-CY domains assessed is provided by Schiariti et al. (2011).

KIDSCREEN-52. The KIDSCREEN-52 is the first generic cross-cultural measure of health-related quality of life (HRQoL) for children and adolescents aged 8 to 18 years (Petersson, Simeonsson, Enskar, & Huus, 2013, p. 3; Ravens-Sieberer et al., 2008). It has sound psychometric properties and is validated in a cross-cultural context (Davis et al., 2010, p. 175; Ravens-Sieberer et al., 2008, p. 646). Ten domains of HRQoL are evaluated including physical well-being, psychological well-being, moods and emotions, self-perception, autonomy, parent relations and home life, social support and peers, school environment, social acceptance, bullying, and financial resources (Sakzewski, Carlon, Shields, Ziviani, & Boyd, 2012, p. 417). A detailed analysis of the ICF-CY domains assessed in the items is provided by Petersson et al. (2013, p. 3). The instrument is available in two versions including a child self-report version

and a parent proxy version where the items are scores on a 5-point Likert-type scale. Rasch scores are computed for each dimension and transformed into T-values (mean = 50, SD =10) with higher scores indicating better HRQoL and well-being (Ravens-Sieberer et al., 2008, p. 647).

3D kinematic measures. 3-dimensional kinematic measures enable objective measurement of kinematics (e.g. trajectories, velocity, acceleration, angles) and kinetics (e.g. forces, joint moments, joint powers), as well as of muscle activity when combined with electromyography (Mercuri, 2011, p. 115). Although 3D kinematic measures have become important instruments in the assessment of gait, the variety, complexity and range of movements of UE function present a major challenge in the interpretation of any kinematic data (Mercuri, 2011, p. 115). Kinematic variables are task-specific, therefore reliability should be established for each new assessment setting. Similarly, any results should be interpreted within the context of the specific task requirements (Schneiberg, McKinley, Gisel, Sveistrup, & Levin, 2010).

Goal Attainment Scale (GAS). GAS in a non-condition specific semi-structured interview used to evaluate individualised goals. It can be used with people of all ages and disabilities, yet variable validity has been reported (Sakzewski et al., 2007, p. 235). Due to inherent bias on the goal setting and evaluation process, it is recommended that the goals should be set and evaluated by a different person than the one giving the intervention (Sakzewski et al., 2007, p. 237). The goals are scored on a 5-point scale. Each goal weighted according to importance and a total T-score is calculated as a weighted average of the scores. A score of 50 indicates that the goals on average are attained, and a score over 50 expressing a better than expected outcome (Sakzewski et al., 2007, p. 235). Concerns have been raised about the appropriateness of the goals set, subjectivity of weighting the goals and generation of the T-score (Sakzewski et al., 2007, p. 238; Wagner & Davids, 2012, p. 1266).

Data collection and analysis

Selection of studies

The literature search was conducted by MT. The titles and abstracts of potentially relevant records were screened; when the abstract did not provide adequate information, or was not available, the full article was retrieved. The full-text of the potentially relevant records was

read and assessed against the inclusion and exclusion criteria. When the results from the same trial concerning the same outcomes of interest were published in two separate articles, only the article with the longest follow-up time was included.

Extraction of descriptive information

Descriptive information of the included trials was extracted by MT.

Evaluation of level of evidence

Each included article was evaluated for the level of evidence by MT and based on the AACPDM system developed from the work by Sackett et al. at the Centre for Evidence Based Medicine (CEBM) (Darrah et al., 2008).

Assessment of quality of conduct

Two independent reviewers (MT, PB) assessed the included trials for methodological rigour using the AACPDM quality of conduct rating scale. When the research group conducted sub-studies within the main trial and published separate articles about trials, the articles were treated independently in the quality of conduct analysis, with a notion on that same participants were used. This decision was made because different research questions and measurement instruments were employed.

The AACPDM rating scale was developed based on existing literature and consensus among clinicians and researchers of the AACPDM Treatment Outcomes Committee, and has acceptable interrater reliability (ICC = 0.76 for the total score; ICC 0.55-0.73 for each individual category) (Wiart et al., 2012, pp. 607, 609). The questions were answered either ‘yes’ or ‘no’. A conduct rate was judged as strong when 6-7 of the questions were answered ‘yes’, moderate when 4-5 of the questions were answered ‘yes’, and weak when 3 or less questions were answered ‘yes’ (Darrah et al., 2008, p. 21). The reviewers were not blinded to the authors, institutions, journal or findings of the articles.

Because of vagueness of question 7 “Considering the potential within the study design, were appropriate methods for controlling confounding variables and limiting potential biases used?”, it was answered based on the trial’s ability to limit four sources of systematic bias

defined in the Cochrane Handbook for systematic reviews (Higgins & Green, 2011, p. 80). These bias included selection bias (systematic differences in comparison groups), performance bias (systematic differences in the care provided apart from the intervention), attrition bias (systematic differences in withdrawals from the trial) and detection bias (systematic differences in outcome assessments) (Higgins & Green, 2011, p. 80). The conduct ratings were discussed, and additional information was acquired until consensus was reached. Robbin Hickman, a contact person for the AACPDM methodology, was contacted for specific questions about the interpretation and scoring of the questions.

Adverse events

The reported adverse events, and the methods used to identify them, were identified by MT.

Reporting of treatment effect

This review deviates from the AACPDM methodology in reporting the treatment effect. The AACPDM methodology advices that statistical significance is used to report the trial results (Darrah et al., 2008, p. 15). However, statistical significance confounds sample size and has little clinical importance (Higgins & Green, 2011, p. 12). In turn, to analyse the (in)consistency of the included trials, the standardised mean difference (SMD) with 95% confidence intervals was calculated for each measurement instrument at each follow-up point. The data was analysed using the Review Manager (RevMan) version 5.2. using SMD as defined in Hedges (adjusted) g. The random effects model was used to allow for the fact that the true effect could vary from study to study. When a measurement instrument was constructed so that a lower value indicated improved outcome, the mean values from the set of data were adjusted for effect direction by multiplying them by -1. The level for statistical significance for set at $p<0.05$. Pooling of the effect sizes was conducted when assessed appropriate and clinically relevant.

In addition, the raw scores of the group mean and standard deviation are given as the mean group pre-post change scores may be used to study whether the scores exceeded a known minimal detectible change (MDC).

Dealing with missing data

Information on trial characteristics was inferred from the included articles. However, when the information was unclear or missing, the methodology articles were reviewed; any information obtained from these was reported. Following advice from the AACPDM committee, no authors were contacted for missing details.

When the trials reported 95% confidence intervals (95% CI) instead of standard deviations (SD), the SD was obtained via methods advised in the Cochrane Handbook for Systematic Reviews (Higgins & Green, 2011, p. 117). In trials with a small sample size (less than 60 in each intervention group), a divisor value from the t distribution was obtained by using degrees of freedom equal to the group sample size minus 1. The SD for each group was then obtained by dividing the length of the CI by the divisor, and multiplying by the square root of the group size: SD = √N x (upper limit - lower limit) / (divisor value from t distribution).

Assessment of heterogeneity

Heterogeneity of the included trials was assessed to decide about the feasibility of pooling the results. Three main aspects were used to guide the decision. First, the primary studies had to have similar, if not identical, research questions or hypotheses. Second, the target population, intervention of interest, the comparator intervention and key outcomes had to be comparable. Third, the dependent and independent variables had to be operationalised in a compatible way (Polit & Beck, 2012, p. 655). If heterogeneity was assessed to be significant, an in-depth narrative analysis of the factors contributing to heterogeneity was conducted.

Reporting bias

The protocols of the included trials and any secondary publications of the same study were compared with the included article for any reporting biases.

Ethical considerations

No universal, internationally accepted standards for ethics in systematic reviews exist (Vergnes, Marchal-Sixou, Nabet, Maret, & Hamel, 2010). A number of steps were taken to ensure ethical quality and objectivity in this thesis, with the most important being provision of a clear account of the steps taken in searching for and treating the existing work in the field.

All original research was throughly studied to avoid misrepresentation of the original findings, and all content of this work was based on the best knowledge of the author.

All data from the included studies was treated on group-level, and no individual-level participant data was used. It was checked that all included primary trials had received acceptance by an ethical committee. Evaluation of reported adverse effects was included in the final evaluation of the data. No commercial, personal or ideological conflicts of interests were disclosed, and no funding was received for this thesis.

Deviations from the protocol

Some deviations from the original study protocol were taken. The inclusion criteria was amended to include children who had received Botox injections in the UE within 6 months prior to study entry and children who had previously undergone CIMT or BIT. This amendment was made because of the limited number of relevant primary studies, and because it could not be assured that these types of participants were excluded in all the relevant primary studies.

The inclusion criteria was amended to include all measurement instruments used to assess the outcomes of interest in the included trials. However, the GAS was not included due to inherent biases on the goal setting and evaluation process. The primary outcomes of interest were defined as bimanual UE function, unimanual UE function and participation in everyday activities. The secondary outcomes of interest were defined as individualised goals and quality of life.

Instead of independently coding the ICF-CY components assessed in each included measurement instrument as indicated in the AACPDM methodology, current literature where the ICF linking rules (Cieza et al., 2005) were employed was consulted. Unfortunately this literature was not available for several of the included measurement instruments and an independent analysis of the ICF-CY levels based on the ICF linking rules was beyond the scope of this systematic review.

4. Results

This chapter provides an account of the main findings in this systematic review.

Identification of studies

The search strategy yielded 2007 records, of which 350 were relevant for further screening. After screening for title and abstract, 336 records were excluded as they clearly did not meet the inclusion criteria. The full text of 14 records was read, with six meeting the inclusion criteria. No additional records were identified from the reference lists of the included records. The selection process is described in detail in figure 3. The research groups conducting the included trials have published multiple articles concerning the same trial with focus on different outcomes of interest and / or different follow-up times. Only the articles with the longest follow-up time were included. A list of the excluded publications is provided as supplementary material III**.**

Study characteristics

The study characteristics of the included trials are presented in table 3. Two trials employed a multi-centre design, while one trial was a single-centre trial. The randomisation process varied with one trial using a cluster-, one a matched-pairs-, and one a stratified randomisation process. The Fedrizzi 2013 trial included a control group of children who received standard occupational or physiotherapy during the intervention. Because the objective of this systematic review was to study the effectiveness of CIMT compared with BIT, only participants in the CIMT and BIT groups were included in any analyses.

In total 178 children with spastic unilateral CP aged 2 to 16 years participated in the trials. Of the total amount of children, 36 participating in the Gordon trial were also included in the sub-studies led by Hung and de Brito Brandao. Using the Manual Ability Classification System (MACS), the Sakzewski and the Gordon trials reported the children's manual ability at levels I to III, with the majority being classified at level I and II. The Fedrizzi trial reported hand function as mild, moderate or severe with the participants being distributed over the categories rather equally.

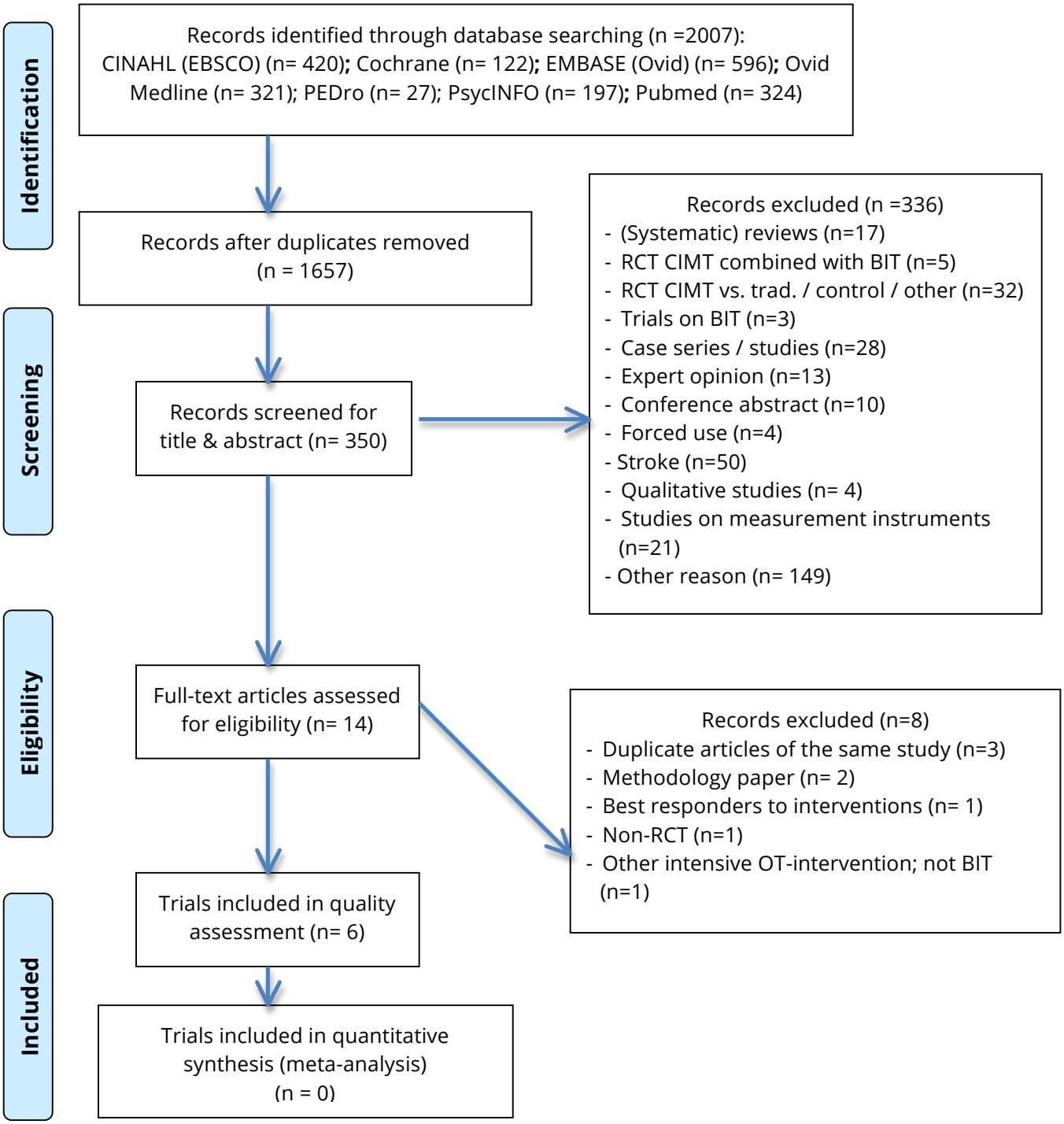

Figure 3. *The study flow diagram.*

Table 3. *Study characteristics.*

Study	RCT design	LE - CR	Follow -up	Participants	N (groups)	CIMT	BIT	MI - primary	MI - secondary
Fedrizzi 2013	Cluster, multicentre	II - 3/7	IP, 12w, 24w	Age: 2 - 8y (mean & SD not given); mild / moderate / severe hand function	72 (39 CIMT, 33 BIT)	10w, 3h/d. 3d at rehab. centre (1.5h with therapist, 1.5h with parents), 4d at home w. parents. Glove worn 3h/d during therapy. Total 210 hrs. RC / home. Italy.	10w, 3h/d. 3d at rehab. centre (1.5h with therapist, 1.5h with parents), 4d at home w. parents. Total 210 hrs. RC / home. Italy.	QUEST, Besta	(several global & developmental scales)
Sakzewski 2011 (INCITE)	Matched-pairs, multicentre	II - 4/7	3w, 26w, 52w	Age: 5 - 16y (10.2±2.7); GMFCS level I-II, MACS I-III	64 (32 CIMT, 32 BIT)	10 weekdays, 6h/d. Glove worn during day camp. Total 60 hrs. Age-grouped community-based day camp. Circus-theme. Australia.	10 weekdays, 6h/d. Total 60 hrs. Age-grouped community-based day camp. Circus-theme. Australia.	MUUL, AHA, COPM	JTTHF, LIFE-H
Sakzewski 2012 (INCITE)	Idem.	II - 4/7	Idem. with Sakzewski et al. 2011					CPQOL-Child, KIDSCREEN-52	
Gordon 2011	Stratified, single-centre	II - 7/7	IP, 4w, 24w	Age: 3.5 - 10y (6.3±2.2); MACS I-III (only 1 child with MACS III per group)	42 (21 CIMT, 21 BIT)	15 weekdays, 6h/d + 1h/d unimanual practice without restraint with caregiver at home during and for 6 mth following intervention (i.e. 360min/w). Sling worn continuously (off <15min/day). Total 90 hrs. Day camp (6 camps between July 2007-09.) USA.	15 weekdays, 6h/d + 1h/d bimanual practice with caregiver at home during and for 6 mth following intervention (i.e. 360min/w). Total 90 hrs. Day camp (6 camps between July 2007-09.) USA.	JTTHF, AHA	QUEST, GAS, activity monitors
Hung 2011	Idem.	II - 1/7	IP only	Age: 4-10y (mean & SD not given); MACS I-II	20 (10 CIMT, 10 BIT)	Idem. with Gordon et al. 2011 - this is a sub-study with the first 20 participants		3D analysis, AHA	
de Brito Brandao 2012	Idem.	II - 2/7	IP only	Age: 3.5-10y (mean & SD not given); MACS I-III	16 (8 CIMT, 8 BIT)	Idem. with Gordon et al. 2011 - this is a sub-study with the last 16 participants		PEDI, COPM	

Abbreviations: *LE = level of evidence; CR = conduct rating; N = total amount of participants; MI = measurement instrument; w = week(s); IP = immediately post-intervention; y = years of age; SD = standard deviation; GMFCS = Gross Motor Function Classification Scale; MACS = Manual Ability Classification System; d = day(s); RC = rehabilitation centre.*

The duration, intensity and overall dose of the intervention varied across the trials. The Sakzewski and Gordon trials employed a program of a shorter duration and higher intensity that was delivered in a day-camp format. The Fedrizzi trial used a less-intensive, longer-duration program that was delivered partly at a rehabilitation centre and partly at home. The overall dose varied from 60 to 210 hours. The type of constraint used in the CIMT groups varied with the Fedrizzi and Sakzewski trials using a glove and the Gordon trial a sling. The constraint was worn from three hours a day to whole day with minor breaks (<15min) being allowed. The Fedrizzi and Gordon trials employed a one-to-one therapist-child ratio with each child having the same therapist during the intervention. The time spend with the therapist varied from 1.5 hours three times a week totalling 45 hours (21% of the total dose) in the Fedrizzi trial to six hours a day totalling 90 hours (100% of the total dose) in the Gordon trial. In addition, in accordance with the group allocation one hour of unimanual practice without the restraint or bimanual practice with a caregiver was included at home during and for six months following the intervention. In the Sakzewski trial four interventionist provided the intervention for all children.

The outcomes of interest in the included trials were bimanual UE function, unimanual UE function, individual goal attainment, participation, and quality of life. In total thirteen different measurement instruments were used with the most common being the AHA, JTTHF, grasp domain of the QUEST and COPM performance scale, all used in two trials each. The MUUL, Besta scale, total score of the QUEST, 3D kinematic analysis of a drawer opening task, PEDI, LIFE-H, COPM satisfaction scale, GAS, activity monitors, CP-QOL Child and KIDSCREEN-52 were all used in one trial each. Because the instruments assessed items across the ICF-CY domains, it was not possible to organise the findings according to the ICF-CY domains.

The follow-up period varied from 24 weeks in the Gordon and Fedrizzi trials to 52 weeks in the Sakzewski trial. The two sub-studies of the Gordon trial conducted follow-up measurements immediately post-intervention only.

Quality of conduct

This systematic review consisted of RCTs capable of producing level II evidence. The quality of conduct of the trials is presented in table 4. One trial was of high quality of conduct, three trials of moderate and two trials of weak quality of conduct. Detailed reasoning for the ratings is provided as supplementary material IV.

Adverse events

The included trials reported on no adverse events. It was reported that children in the CIMT groups tolerated wearing the constraint well.

Treatment effects

The observed treatment effects are presented in tables 5, 6 and 7. Table 5 presents the findings for the primary outcomes of interest of this review when the measurement instruments had good, established psychometric properties. Table 6 lists the findings when adequate psychometric properties for the measurement instruments could not be established, or when sufficient information was not available. Table 7 displays the findings for the secondary outcomes of interest of this review. The ICF-CY domains assessed on each measurement instrument are indicated in the tables. A negative SMD indicates a result favouring CIMT. The findings for the primary and secondary outcomes of interest are discussed below.

Bimanual UE function

Measuring bimanual ability with the AHA the Gordon 2011 and Sakzewski 2011 trials observed no or minimal difference between the CIMT and BIT groups up to 52 weeks follow-up (table 5). The 95%CI were consistently wide. Measured on the bimanual domain of the Besta scale, the Fedrizzi 2013 trial observed a small difference between the groups with the SMD favouring BIT in all follow-ups (table 6).

The Hung 2011 trial assessed bimanual function with 3D kinematics. Because it was not possible to confirm the validity of the kinematic measures used, nor the operationalisation of the definitions for bimanual coordination, the results of this trial were not included in any further analyses. As discussed by Schneiberg et al. (2010, p. e167), kinematic variables are

Table 4. *Scoring of the quality of conduct.*

Trial	LE	Inclusion & exclusion criteria	Intervention description & adherence	Valid & reliable measurement instruments	Blinding of assessors	Statistical evaluation & power	Drop-outs <20% and balanced	Control of confounding variables	Total QC
Fedrizzi 2013	II	yes	no	no	yes	yes	yes	no	4 / 7
Sakzewski 2011	II	yes	no	yes	no	yes	yes	no	4 / 7
Sakzewski 2012	II	yes	no	yes	no	yes	yes	no	4 / 7
Gordon 2011	II	yes	yes	yes	yes	yes	yes	yes	7 / 7
de Brito Brandao 2012	II	no	no	yes	no	no	yes	no	2 / 7
Hung 2011	II	no	no	no	yes	no	no	no	1 / 7

Abbeviations: *LE = level of evidence; QC = quality conduct.*

The AACPDM quality of conduct questions

1. *Were inclusion and exclusion criteria of the study population well described and followed?*
2. *Was the intervention well described and was there adherence to the intervention assignment? (for 2-group designs, was the control exposure also well described?) Both parts of the question need to be met to score 'yes'.*
3. *Were the measures used clearly described, valid and reliable for measuring the outcomes of interest?*
4. *Was the outcome assessor unaware of the intervention status of the participants (i.e., were the assessors masked)?*
5. *Did the authors conduct and report appropriate statistical evaluation including power calculations? Both parts of the question need to be met to score 'yes'.*
6. *Were dropout/loss to follow-up reported and less than 20%? For 2-group designs, was dropout balanced?*
7. *Considering the potential within the study design, were appropriate methods for controlling confounding variables and limiting potential biases used?*

task-specific, and the validity and reliability must therefore be established for each kinematic measure separately.

Unimanual UE function

Measuring unimanual function with the MUUL, a SDM 0.22 [95%CI -0.28 to 0.72; p=0.38] favouring BIT was observed at 3 weeks follow-up, and SMD 0.46 [95%CI -0.06 to 0.99; p=0.08] favouring BIT at 52 weeks follow-up (table 5). No to minimal difference between CIMT and BIT was observed when unimanual UE function was measured with the JTTHF in the Sakzewski 2011 and Gordon 2011 trials up to 52 weeks follow-up (table 6). A difference of SMD -0.36 [-0.83, 0.12; p=0.14] favouring CIMT was observed on the total score of the QUEST immediately post-intervention in the Fedrizzi trial (table 6). However, the difference was not maintained at other follow-ups.

Small SMDs favouring CIMT were observed when grasp was measured on the grasp domain of the QUEST immediately post-intervention in the Fedrizzi trial and 4 weeks follow-up in the Gordon trial, as well as on the grasp domain of the Besta scale immediately post-intervention (table 6). The differences were not fully maintained at further follow-ups.

Participation

No to minimal differences between CIMT and BIT were observed when participation was measured on the LIFE-H personal care and recreation domains in the Sakzewski 2011 trial (table 5). The 95%CIs were consistently wide. Measuring participation in ADLs on the PEDI self-care domain and the independence scale, a SMD of 0.57 [95%CI = -0.44 to 1.58; p=0.24] and SMD 0.41 [95%CI =-0.58 to 1.41; p=0.40], respectively, favouring BIT was observed immediately post-intervention in the de Brito Brandao 2012 trial (table 5). A small SMD favouring BIT was observed when participation was measured with the ADLs domain of the Besta at all follow-up points in the Fedrizzi 2013 trial (table 6).

Individualised goals

No difference between CIMT and BIT was observed when individualised goals were measured with the COPM performance domain up to 52 weeks follow-up in the Sakzewski trial with

moderate quality of conduct (table 7). The 95%CIs were wide. Large SMDs with very wide 95%CIs were observed in the de Brito Brandao 2012 trial with low quality of conduct (table 7).

Quality of life

The Sakzewski 2012 trial measuring quality of life was not included in any further analyses in this review. This decision was taken the article did not provide raw scores with standard deviations or 95% confidence intervals, making calculation of SMDs not possible. It was not possible to interpret of the strength of the EMD in relation to the maximal possible change in the scores.

Synthesis of results

Based on the heterogeneity of the included trials, pooling of the results from the included trials was judged to be of little value. No measurement instrument was used in more than two trials, and the dosing of the intervention as well as the follow-up times varied.

Table 5. *Effect of CIMT compared with BIT in children with unilateral CP in bimanual UE function, unimanual UE function and participation in everyday activities when measured with instruments with good, established psychometric properties. A negative SMD favours CIMT. Note that Sakzewski (2011) reported the AHA scores on the 0-100 scale and Gordon (2011) on the logit scale.*

Outcome of interest	Measurement instrument	ICF-CY domains	Study LE - QC	Follow-up, w	n	CIMT mean (SD)	n	BIT mean (SD)	SMD (95%CI) *(random effects)*	p
Bimanual UE function	AHA	A or A-BF 78%; BF 23% (Hoare 2011)	Sakzewski 2011 II-4/7	pre	32	61.7 (12.6)	32	63.0 (12.8)		
				3	32	64.8 (13.1)	30	64.9 (11.5)	0.01 [-0.48, 0.50]	0.97
				26	29	63.0 (13.9)	29	65.3 (11.5)	0.18 [-0.34, 0.69]	0.50
				52	30	64.1 (11.7)	27	65.7 (12.6)	0.13 [-0.30, 0.65]	0.62
			Gordon 2011 II-7/7	pre	21	0.38 (1.75)	21	0.38 (1.74)		
				0		0.80 (1.72)		0.94 (1.71)	0.08 [-0.53, 0.69]	0.79
				4		0.90 (1.70)		0.99 (1.53)	0.05 [-0.55, 0.66]	0.86
				24		1.05 (1.49)		0.94 (1.71)	-0.07 [-0.67, 0.54]	0.82
Unimanual UE function	MUUL	A 3%; A or A-BF 43%; BF 51% (Hoare 2011)	Sakzewski 2011 II-4/7	pre	32	67.1 (12.4)	32	70.8 (11.2)		
				3	32	69.0 (12.4)	30	71.5 (9.7)	0.22 [-0.28, 0.72]	0.38
				26	29	71.1 (11.7)	29	71.0 (11.0)	-0.01 [-0.52, 0.51]	0.98
				52	30	68.9 (12.4)	27	74.6 (11.8)	0.46 [-0.06, 0.99]	0.08
Participation in everyday activities	PEDI self-care	Concepts on A&P 113; BF 14; E 84 (Ostensjo 2006)	de Brito Brandao 2011 II-2/7	pre	8	58.1 (6.5)	8	60.1 (6.1)		
				0		60.1 (6.1)		63.5 (5.0)	0.57 [-0.44, 1.58]	0.24
	PEDI Independence	NA		pre		28.9 (7.5)		30.5 (4.8)		
				0		29.1 (7.3)		31.8 (4.4)	0.41 [-0.58, 1.41]	0.40

Participation in everyday activities & social roles	LIFE-H (LF) Personal care	A & P (Sakzewski 2011, Adolfsson 2011)	Sakzewski 2011 II-4/7	pre	32	7.1 (1.9)	32	7.2 (1.4)		
				3	32	7.6 (2.0)	30	7.8 (1.3)	0.12 [-0.38, 0.61]	0.65
				26	29	7.9 (1.5)	29	8.0 (1.2)	0.07 [-0.44, 0.59]	0.79
				52	30	7.9 (1.7)	27	8.1 (1.3)	0.13 [-0.39, 0.65]	0.62
	LIFE-H (LF) Recreation	A & P (Sakzewski 2011, Adolfsson 2011)	Sakzewski 2011 II-4/7	pre	32	7.8 (2.3)	32	7.0 (1.8)		
				3	32	7.6 (2.2)	30	7.4 (2.2)	-0.09 [-0.59, 0.41]	0.72
				26	29	8.0 (2.1)	29	8.3 (2.2)	0.14 [-0.37, 0.64]	0.59
				52	30	7.4 (2.2)	27	7.9 (1.7)	0.25 [-0.27, 0.77]	0.35

Abbreviations: *w = weeks; LE = level of evidence; QC = quality of conduct; n = number of participants in the subgroups; LIFE-H (LF) = long-form; A & P = ICF activity & participation domain; BF = ICF body functions domain.*

Table 6. *Effect of CIMT compared with BIT in children with unilateral CP in bimanual UE function, unimanual UE function and participation in everyday activities when measured with instruments for which adequate psychometric properties could not be established, or where this information was lacking. A negative SMD favours CIMT.*

Outcome of interest	Measurement instrument	ICF-CY domains	Study LE - QC	Follow-up, w	n	CIMT mean (SD)	n	BIT mean (SD)	SMD (95%CI) (random effects)	p
Bimanual UE function	Besta bimanual	not available	Fedrizzi 2013 II-4/7	pre	39	2.54 (0.88)	32	2.67 (0.87)		
				0		2.76 (0.80)		2.94 (0.81)	0.22 [-0.25, 0.69]	0.35
				12		2.74 (0.86)		2.93 (0.86)	0.22 [-0.25, 0.69]	0.36
				24		2.77 (0.84)		3.05 (0.86)	0.33 [-0.14, 0.80]	0.17
Bimanual & unimanual UE function	Besta global score	not available	Fedrizzi 2013 II-4/7	pre	39	2.41 (0.8)	32	2.54 (0.88)		
				0		2.62 (0.75)		2.74 (0.87)	0.15 [-0.32, 0.62]	0.53
				12		2.66 (0.84)		2.8 (0.92)	0.16 [-0.31, 0.63]	0.51
				24		2.66 (0.83)		2.86 (0.90)	0.23 [-0.24, 0.70]	0.33

Outcome of interest	Measurement instrument	ICF-CY domains	Study LE - QC	Follow-up, w	n	CIMT mean (SD)	n	BIT mean (SD)	SMD (95%CI) (random effects)	p
Unimanual UE function	JTTHF	not available (Scoring is based on speed of movement which currently is not classified on the ICF-CY.)	Sakzewski 2011 II-4/7	pre	32	365.7 (198.5)	32	323.0 (168.5)		
				3	32	337.5 (203.8)	30	306.8 (179.8)	0.16 [-0.33, 0.65]	0.52
				26	29	307.9 (190.0)	29	287.4 (177.3)	0.11 [-0.41, 0.63]	0.67
				52	30	285.3 (196.9)	27	282.0 (180.3)	0.02 [-0.50, 0.54]	0.95
			Gordon 2011 II-7/7	pre	21	374.8 (232.5)	21	380.8 (232.5)		
				0		233.1 (173.8)		249.6 (173.8)	-0.09 [-0.70, 0.51]	0.76
				4		207.1 (134.0)		236.9 (133.9)	-0.22 [-0.83, 0.39]	0.48
				24		221.0 (155.6)		222.7 (155.5)	-0.01 [-0.62, 0.59]	0.97
Unimanual UE function	QUEST total score	- Dissociative movements: A - BF 21%; BF 79% - Weight-bearing: A-BF 8%; BF 92% - Protective extension: BF 100% - Grasp: A 7%; BF 93% (Hoare 2011)	Fedrizzi 2013 II-4/7	pre	39	69.4 (15.8)	32	66.3 (20.3)		
				0		76.3 (14.9)		70.0 (20.3)	-0.36 [-0.83, 0.12]	0.14
				12		73.8 (16.7)		71.4 (19.1)	-0.13 [-0.66, 0.33]	0.57
				24		76.1 (15.2)		74.6 (18.3)	-0.09 [-0.56, 0.38]	0.71
Unimanual UE function: grasp	QUEST grasp domain	QUEST grasp domain: A 7%; BF 93% (Hoare 2011)	Gordon 2011 II-7/7	pre	21	69.5 (13.0)	21	68.6 (13.0)		
				0		80.6 (10.8)		79.9 (9.8)	-0.07 [-0.67, 0.54]	0.83
				4		81.2 (9.8)		76.2 (13.4)	-0.42 [-1.03, 0.19]	0.18
				24		78.8 (13.4)		79.4 (10.5)	0.05 [-0.56, 0.65]	0.87
			Fedrizzi 2013 II-4/7	pre	39	65.1 (16.8)	32	64.2 (21.3)		
				0		72.1 (18.8)		66.9 (22.1)	-0.25 [-0.72, 0.22]	0.29
				12		70.8 (18.7)		67.6 (20.7)	-0.16 [-0.63, 0.31]	0.50

Outcome of interest	Measurement instrument	ICF-CY domains	Study LE - QC	Follow-up, w	n	CIMT mean (SD)	n	BIT mean (SD)	SMD (95%CI) (random effects)	p
				24		69.2 (18.7)		68.9 (24.0)	-0.01 [-0.48, 0.45]	0.95
Unimanual UE function: grasp	Besta grasp domain - more affected side	not available	Fedrizzi 2013 II-4/7	pre	39	2.85 (0.77)	32	2.80 (0.91)		
				0		3.15 (0.66)		2.88 (0.86)	-0.35 [-0.82, 0.12]	0.14
				12		3.13 (0.70)		2.95 (0.91)	-0.22 [-0.69, 0.25]	0.35
				24		3.12 (0.71)		3.01 (0.91)	-0.13 [-0.60, 0.33]	0.57
Participation in everyday activities	Besta ADL	not available	Fedrizzi 2013 II-4/7	pre	39	2.14 (0.92)	32	2.40 (1.00)		
				0		2.28 (0.86)		2.59 (0.99)	0.31 [-0.12, 0.75]	0.16
				12		2.40 (0.95)		2.70 (1.03)	0.30 [-0.17, 0.77]	0.21
				24		2.39 (0.93)		2.73 (0.97)	0.34 [-0.11, 0.79]	0.14

Abbreviations: *w = weeks; LE = level of evidence; QC = quality of conduct; n = number of participants in the subgroups; A = ICF activity domain; P = ICF participation domain; BF = ICF body functions domain.*

Table 7. *Effect of CIMT compared with BIT in children with unilateral CP in individualised goals. A negative SMD favours CIMT.*

Outcome of interest	Measurement instrument	ICF-CY domains	Study LE - QC	Follow-up, w	n	CIMT mean (SD)	n	BIT mean (SD)	SMD (95%CI) (random effects)	p
Individualised goals	COPM performance	A & P	de Brito Brandao 2011 II-2/7	pre	8	3.95 (1.25)	8	3.56 (0.66)		
				0		5.54 (1.7)		6.58 (1.19)	0.56 [-0.45, 1.56]	0.26
	COPM parent satisfaction			pre		4.14 (1.54)		4.03 (0.92)		
				0		5.68 (2.06)		6.78 (1.64)	1.10 [-0.72, 2.92]	0.26
Individualised goals	COPM performance	A & P	Sakzewski 2011 II-4/7	pre	32	3.4 (1.0)	32	3.5 (1.2)		
				3	32	6.3 (1.9)	30	6.3 (1.5)	0.00 [-0.50, 0.50]	1.00
				26	29	6.1 (2.0)	29	6.2 (1.7)	0.05 [-0.46, 0.57]	0.84
				52	30	6.5 (2.1)	27	6.6 (1.7)	0.05 [-0.47; 0.57]	0.85

Abbreviations: w = weeks; LE = level of evidence; QC = quality of conduct; n = number of participants in the subgroups.

5. Discussion

An explorative systematic review was conducted with the aim to examine the effectiveness of constraint-induced movement therapy (CIMT) compared with bimanual intensive training (BIT) across the ICF-CY domains in children with unilateral CP. The results from this review provide a means to study the quality of conduct and the consistency of the findings across the primary trials. The results give indications of the effectiveness of CIMT compared with BIT at group-level; they do not on their own constitute the complete evidence needed to make decisions about which intervention to choose for upper extremity training for any individual child with spastic unilateral CP. In line with the definition of evidence-based practice, the results should be considered together with the preferences of the child and his or her family, as well as the expertise and practice knowledge of the involved therapist(s).

Summary of evidence

The evidence gathered in this systematic review consists of six randomised controlled trials, one with high, three with moderate and two with weak quality of conduct. Each trial included 42 to 71 participants, making the trials relatively large in this area of research. An exemption was the two small sub-studies in the Gordon 2011 trial. Overall, based on three trials with moderate to high quality of conduct, it is not possible to confidently say that CIMT or BIT is more effective than the other in improving bimanual UE function, unimanual UE function and participation in children with unilateral CP at any follow-up up to 52 weeks post-intervention. The 95% confidence intervals were wide and overlapped the null value in all results, indicating inaccurate precision of the findings; if the study was repeated, there would be a 95% chance that the group mean would land within the 95%CI. Therefore, the result may just as well favour CIMT as it could favour BIT.

The only small differences in the post-scores between the groups were observed in unimanual UE function and achievement of individualised goals. One trial with moderate quality of conduct observed a small difference in unimanual UE function measured with the MUUL favouring BIT at 52 weeks follow-up. Based on observations from two trials with moderate and high quality of conduct, CIMT showed a tendency to be slightly more effective

than BIT in improving grasp function of the affected UE when measured immediately or shortly after the intervention. However, the difference was not maintained at 24 weeks follow-up, and the 95%CI overlapped the null value at all follow-up points indicating inaccurate precision of the finding.

One trial with 16 participants observed a large effect favouring BIT in attainment of individualised goals measured with the COPM. In comparison, a trial with moderate quality of conduct and 64 participants observed no difference between CIMT compared with BIT in attainment of individualised goals. The smaller trial the trial was of poor quality of conduct, and systematic errors may have influenced the results. For instance, the parents were not blinded to their child's group allocation, and this may have led to the parents choosing goals that better reflect the interventions they child was allocated to leading to unnecessary bias. From a practical standpoint, concealing allocation up to the point of assignment is always possible, regardless of the research question (Higgins & Green, 2011, p. 81).

The findings at group-level did not support the hypothesis of training specificity where CIMT was anticipated to be more effective in improving unimanual UE function and BIT being more effective in improving bimanual UE function. Neither do the findings do fully agree with the systematic review by Dong et al. (2013, p. 10) in which the conclusion was that "CIMT is more effective in improving paretic arm function, whereas BIT leads to more improvement in bimanual and functional tasks". The review based its conclusion on a narrative analysis of the findings in the included trials, and did not provide any indication of the size of the treatment effects.

The SMD in this systematic review was calculated as the mean difference between the interventions at each follow-up point. However, it is interesting to note that the mean group pre-post change scores exceeded a known minimal detectible change (MDC) only when attainment of individualised scores was measured with the COPM. The observation applies to both groups in the Sakzewski 2011 trial, and to the BIT group in the de Brito Brandao 2012 trial. In the Gordon 2011 trial the mean group pre-post change scores exceeded a known MDC when grasp of the affected UE was measured with the grasp domain of the QUEST.

However, the MDC was calculated for the the total QUEST score, and may is not directly applicable in the individual domains.

No information of the MDC was currently available for many of the measurement instruments. In general, a change of 10 - 30% has been proposed to indicate minimal clinically important change (van Tulder, Malmivaara, Hayden, & Koes, 2007), a term used interchangeably with MDC. Measuring unimanual UE function with the JTTHF, the mean group scores improved 37.8% for CIMT and 34.5% for BIT from baseline to immediate post-intervention follow-up in the Gordon 2011 trial. Further, small improvements were observed in both groups at 24 weeks follow-up. In the Sakzewski 2011 trial the mean group scores on the JTTFH improved 22% for CIMT and 12.7% for BIT from baseline to 52 weeks follow-up. These findings may indicate that both CIMT and BIT were effective in improving speed of movement.

Analysis on the ICF-CY domains

As the majority of the measurement instruments used in the included trials assessed items spread across the ICF-CY domains, it was not possible to organise the analyses in this systematic review on the structure of the ICF-CY. No literature where the ICF-CY domains on the instruments was available for several of the measurement instruments, especially when the analysis was based on the ICF linking rules. Neither was it possible to conduct analyses about possible linkages between the ICF-CY domains, as advocated in the AACPDM methodology. With the instruments assessing items across the ICF-CY domains, any analyses of linkages between the domains would require a full set of raw data so that the scores for the specific items could be extracted.

As noted by Hoare et al. (2011, p. 988), inconsistent analyses of the ICF-CY domains assessed in different measurement instruments have contributed to inconsistencies in the analysis of findings in interventions. This holds especially true for measurement instruments that appear to assess items across more than one ICF-CY domain. The ICF linking rules have been developed by Cieza et al. (2005) to provide a standardised method for the analysing the measurement instruments. Even so, different interpretations are still made, see for instance analyses of UE measurement instruments by Hoare et al. (2011) and Schiariti (2014). This

should be born in mind when considering the ICF-CY domains reported for each measurement instrument in this review. One factor contributing to the inconsistent analyses seems to be related to which aspects of the items are analysed. Although many items in the instruments are administered within the context of functional activities, it is the specific scoring criteria, rather than the outcome of the activity itself, that provides the basis for analysis of the ICF-CY categories (Hoare et al., 2011, p. 988).

Exploring the factors possibly influencing the children's response

In general, similar results were observed regardless of whether the interventions were delivered as a shorter duration and higher intensity program, as in the Gordon and Sakzewski trials, or a less-intensive, longer-duration program, as in the Fedrizzi trial. However, apart from the grasp domain of the QUEST, the trials used different measurement instruments, making it difficult to draw conclusions about the effectiveness of the training intensity. The SMDs were low with wide 95%CIs when bimanual UE function was measured with the AHA and unimanual UE function with the JTTHF in trials providing 60 and 90 hours of interventions. Similarly, the SMDs were low with wide 95%CIs when unimanual function was measured with the grasp domain of the QUEST in trials providing 90 and 210 hours of interventions. Currently, it remains unclear whether the high intensity or more distributed models of CIMT and BIT lead to more improvements in the outcomes of interest (Eliasson et al., 2013, p. 7). Apart from the Gordon trial that reported a complete adherence confirmed by direct observation by supervisors and daily logs, the adherence to the intervention was not reported in the trials included in this review.

With the low prevalence of CP and the heterogenous presentation make it challenging to compose comparable groups in trials concerning children with CP (Kunz et al., 2006, p. 1240). Two of the included trials in this review based allocation the participants on characteristics such as age, sex, side of hemiplegia, and UE function with the aim to minimise baseline differences and to improve chances that the findings reflect the interventions and not differences in the characteristics of the participants. The Sakzewski trial used matched-pairs RCT design and the Gordon trial a stratified design. The heterogeneous group of participants may have lead to increased variance in the mean group scores, which would then be reflected in the wide 95% confidence intervals.

The age of the participants in the included trials varied from two to sixteen years. Although previous research has suggested that younger children may benefit from intensive UE training more than older children in terms of bimanual performance (Sakzewski et al., 2011a, p. 668), current evidence indicates inconsistent results in whether age correlates with outcomes achieved with CIMT (Eliasson et al., 2013, p. 8). A post-hoc study of the best responders in the Sakzewski 2011 trial found that younger children did not achieve greater improvements in UE function than older children, and that older children were more likely to achieve favourable outcomes in individualised goals (Sakzewski et al., 2011, p. 582). Best responders in the study were defined as those children who achieved a score exceeding the MDC or CMD.

From a theoretical standpoint, providing the children with an intensive intervention at critical periods of brain development may provide a better response to the intervention. Data from a longitudinal study indicate that well-functioning children under the age of three have the highest rate of development of bimanual activities, and that the development of the affected UE seems to plateau at seven years of age (Holmefur et al., 2010). Where as adults presenting with learned non-use have once experience what it is like to use the affected UE effectively, children with unilateral CP do not have this experience. As the development of motor control is based on use and experience, activity-dependent developmental periods may provide a window for teaching the children to use their more affected UE more effectively (Boyd et al., 2010, p. 2).

Recently, much focus has been directed to studying the whether impairments in body structures, especially the laterality of the corticospinal tract projections and the type of brain lesion, have predictive value on the effect of CIMT in children with unilateral CP (Friel, Kuo, Carmel, Rowny, & Gordon, 2014; Inguaggiato, Sgandurra, Perazza, Guzzetta, & Cioni, 2013; Islam et al., 2014; Juenger et al., 2013; Rickards et al., 2014; Staudt & Berweck, 2014; Sterling et al., 2013). This is interesting as voluntary skilled movement is dependent of corticospinal tract function in humans. Based on smaller scale studies, it has been postulated that CIMT may lead to different kind of exercise-induced neuroplasticity in children with ipsilateral corticospinal tract (CST) projections (the CST in the ipsilateral hemisphere sends signals to the motor units of the involved hand) versus children who have typical contralateral projections.

However, a recent trial by Islam et al. (2014) explored the changes in cortical organisation and UE function measured with the AHA, MUUL and JTTHF and concluded that improved UE function was found after CIMT regardless of the CST projection patterns and brain lesion characteristics. Similar findings were observed after BIT (Friel et al., 2014). These findings emphasises that the variation in the children's response to intensive UE training is multifactorial, and that the CST projection pattern cannot on its own explain the children's response to CIMT, although it may affect the response to some degree (Eliasson et al., 2013, p. 9; Sakzewski et al., 2011).

ICF contextual factors

As discussed above, children's response to CIMT and BIT involves a complex interplay between aspects of functioning at the ICF-CY body functions, body structures and activity & participation domains. Personal factors, comprising of features of the individual that are not part of a health condition or health state (WHO, 2001; Rosenbaum & Stewart, 2004, p. 9), may either facilitate or be barriers to the children's response to the intervention. Motivation has been identified as the only characteristic unrelated to health state that influences change in function in children with CP (Bartlett & Palisano, 2002; Miller, Ziviani, Ware, & Boyd, 2014a, p. 1). A recent study by Miller et al. (2014a; 2014b) examined the extend to which mastery motivation, defined as the driving force that provides persons with the incentive and encouragement to independently act, explore, and attempt to master moderately challenging tasks, affected the outcomes of CIMT and BIT in children with unilateral CP. The study observed that, in general, the children's persistence with tasks significantly affected the measured outcomes, especially the attainment of individualised goals measured with the COPM. Further, the level of mastery motivation has been associates with better readiness to learn as well as better achievement of ADLs, social communication, and psychological wellbeing (Miller et al., 2014b, p. 267).

Similarly, environmental factors, comprising of the physical, social and attitudinal environments in which people live (WHO, 2001; Rosenbaum & Stewart, 2004, p. 9), may facilitate or impede the response. The Miller et al. (2014a, 2014b) study found that consistent, positive feedback and discipline from parents was associated with higher level mastery motivation and task persistence. In contrast, in children with mild UE impairment, age, sex,

limitations in manual ability and movement were not found to significantly contribute to mastery motivation (Miller et al., 2014b, p. 268). Essentially, because participation relies on a complex interplay between the child, the family and environmental factors, it could be assumed that changing child factors alone in an activity-based intervention may have little impact on participation (Sakzewski et al., 2011b, p. 532).

Are we measuring the right outcomes?

Although the post-hoc analyses in the Sakzewski trial indicate a large variation in the children's response to CIMT and BIT, the group-level results suggest that subtle gains in unimanual UE function in the CIMT group were not always transferred to improvements in bimanual UE function. This finding follows the argumentations that the relationship between hand impairments and manual ability is not predictable in a straightforward way (Arnould, Penta, & Thonnard, 2007, p. 708; Boyd et al., 2010, p. 2), and that it is not clear as to what extend impairments of body functions and structures translate to activity limitations and participation restrictions. In their post-hoc analysis of the best responders to CIMT and BIT, Sakzewski et al. (2011, p. 583) observed a tendency that a change in movement efficiency of the impaired UE was associated with better improvement in bimanual performance, yet, a change in bimanual performance was not a predictor of improved unimanual UE function. How impairments in body functions and limitations in activity and participation are associated with concepts such as quality of life is unclear (Penta et al., 2001, p. 1627). The complexity of the factors associated with manual ability makes assessment of effectiveness of UE intervention a challenge.

The outcome measures used to assess the efficiency of any intervention must address the aims of the intervention (Cieza et al., 2005, p. 213; Hoare et al., 2011, p. 988; Eliasson et al., 2013, p. 10). CIMT and BIT are based on task-oriented practice with focus on completion of activities rather than on correction of movement patterns and prevention of compensations (Gordon, 2014). However, the majority of the instruments currently available to measure UE function in children with unilateral CP contain many items on the ICF-CY body functions and structures domain. As CIMT and BIT aim to alleviate developmental disregard, defined as spontaneous use of the affected UE, both performance-based instruments, assessing what the child does in his or her habitual environment, and capacity-based instruments, assessing

what the child does in a standardised environment, must be used to attain information of the effectiveness of the interventions in this area. Focusing on individualised goals identified as important by children and their caregivers provides a means to assess meaningful activities for the child, an integral aspect of CIMT and BIT (Sakzewski et al., 2014, p. e193).

One commonly used instrument to measure the effect of these interventions is the QUEST. The QUEST was developed based on neuro-developmental theories, making its basic theoretical construct rather different from that of CIMT and BIT. It is therefore questionable as to what extend the instrument is able to reflect changes in hand function after CIMT and BIT. A longitudinal study observed that impairments underlying many of the QUEST items are unlikely to improve through task-related practice (Hanna et al., 2003). Although the content of the Besta scale has not been analysed using the ICF linking rules, the scoring of the grasp and bimanual function domains is based on variability and stereotypy of movement patterns. For example, the grasp domain is based on the type of grasp [0 = inability to grip cube; 1 = grasping or whole-hand grip; 2 = radial or three-finger grip; 3 = pincer grip (Fedrizzi et al., 2003, p. 86)], making the extend to which is it able to capture change in UE function after CIMT and BIT doubtful. The scoring on the JTTHF is completely based on speed of movement, which currently is not classified on the ICF-CY. How, and to what extend, speed of movement indicates improvements in manual ability is unclear. Together with fluency in movement, accuracy (end-point of the movement), strength regulation, muscle tone, tremor, speed of movement has been analysed to be one of the core aspects of coordination of movement (Janssen et al., 2012).

Transferring manual ability to daily life

To assist integration of improvements in unimanual UE function to bimanual activities in the person's habitual environment, a transfer package is an important aspect of adult CIMT. As Taub & Uswatte (2014, pp. e215-216) point out, the transfer package has been omitted in paediatric CIMT. Of the included trials in this review, only the Gordon trial employed a post-intervention home training program that included practice of bimanual tasks for both groups. However, because the trial did not include a subgroup of CIMT that did not practice bimanual tasks at home, it is not possible to analyse the effect of the home training. Recently, a "hybrid" model of CIMT, where a period of CIMT is combined with a period of BIT, has been introduced

with the aim to incorporate the newly gained unimanual UE function into ADLs requiring use of the two hands (Aarts, Jongerius, Geerdink, van Limbeek, & Geurts, 2010). Whereas trials have been conducted to compare the hybrid model to conventional occupational or physical therapy, to date, only one trial (Deppe et al., 2013) has compared hybrid-CIMT to BIT.

Limitations & strengths

The evidence in this systematic review consists of level II evidence based on the AACPDM classification of evidence levels, this because the included RCTs consisted of less than 100 participants. Larger RCTs have better power to produce more precise estimations of the treatment effect. Based on their power calculations, only the Sakzewski and the Gordon trials met 80% power to detect a meaningful difference between the groups (see supplementary material IV, question 5). The most prevalent methodological shortcomings in the primary studies included 1) lack of reporting of adherence and exposure to the intervention assignment, 2) insufficient control of confounding factors and limitation of potential bias, and 3) non-blinding of the outcome assessor. In addition, the validity, reliability and responsiveness of several of the measurement instruments used were insufficient, or could not be established from current systematic reviews. No measurement instrument was used in more than two studies, making it difficult to extensively compare the study results.

Although an extensive literature search was conducted in multiple databases and the reference lists of all relevant articles were searched, some relevant trials may have been missed because of different terminology used of the interventions. The search strategy was limited to trials explicitly using the terms CIMT and BIT. Only the author assessed the eligibility of the trials against the inclusion and exclusion criteria, introducing a possible selection bias. The quality of conduct in the primary trials was assessed by two independent reviewers both with master's degree education in physiotherapy. The final quality of conduct ratings were reached by consensus, no interrater reliability was calculated. To account for introducing unnecessary bias, reasoning for the quality of conduct ratings was explicitly provided as part of the supplementary material. To ensure correct interpretation of the quality of conduct questions, a contact person for the AACPDM methodology was contacted. One of the questions (question 7) was judged to be too vague, therefore, additional criteria was added to answer the question. The criteria was based on different aspects of bias, as described in the

Cochrane Handbook (see methods). Conducting independent analyses of the ICF-CY domains assessed on the different measurement instruments was beyond the scope of this review. When available, literature applying the ICF linking rules by Cieza (2005) was consulted. It was acknowledged that the interpretation of the ICF linking rules among different authors may vary. However, the use of the ICF linking rules was considered essential as they provide with a structured, standardised way to analyse the outcomes measured on the different instruments.

The data from the primary studies was extracted and analysed by the author. Although the data was double and triple-checked, possible mistakes in the transfer and handling of the data may have occurred. Only data directly available from the publications was used and no authors were contacted for missing or additional information. The calculation of the SMDs and the subsequent analyses were based on a comparison of the group mean scores at each follow-up point, not on an analysis based on mean group changes from the baseline. Although an analysis based on the mean pre-post change scores may be more efficient and powerful in some situations, it requires that the standard deviation of change is reported, which very often is not the case (Higgins & Green, 2011, p. 9.4.5.2). That the final values were used to calculate SMDs must be considered when interpreting the findings in this review. To account for the small sample sizes, the SMD was calculated using Hedges' adjusted g. The baseline scores between the groups differed in for some measurement instruments, for instance, the baseline score in the JTTFH in the Sakzewski trial varied between the groups and where as the pre-first follow-up score improved more in the CIMT group, the SMD favoured BIT as the group mean was better.

Implications for practice

Based on the current evidence from RCTs, it is not possible to confidently say that CIMT or BIT is more effective than the other in improving bimanual UE function, unimanual UE function, participation and individual goals in children with unilateral CP at group-level. As observed with the wide 95% confidence intervals, the estimations of the mean differences between the groups are imprecise. In general, similar results were observed regardless of whether the interventions were delivered as a shorter duration and higher intensity program, or as a less-intensive, longer-duration program. Decisions about which UE intervention could be most

beneficial for a child with unilateral CP should be based on the preferences of the child and the family, as well as on the expertise and practice knowledge of the therapist. Searching for evidence from studies on best responders to CIMT and BIT may provide useful indications as to the choice of the intervention. Measuring treatment effects with individualised goals would enable measurement of aspects of manual ability that reflect meaningful tasks for the child in his or her daily life, and may therefore improve the child's motivation to master the tasks.

The findings imply that manual ability in children with unilateral CP is dynamic, and may be improved by intensive task-oriented practice. However, based on the observations in this review, gains in unimanual UE function cannot be expected to always be transferred to bimanual UE function or to other situations in daily life. When training with intensive focus on the more affected UE is indicated, integration of a period of bimanual training should be considered so that the newly gained unimanual skills may be incorporated in bimanual tasks.

Implications for research

The findings do not indicate that conducting another large RCT comparing CIMT with BIT would result in larger SMDs and more precise confidence intervals. Instead, smaller studies focusing on analyses on best responders would provide clinicians and families with more relevant information for making evidence-based decisions about the type of UE intervention most indicated for each individual child. The findings from the post-hoc analyses on best responders analyses conducted for the Sakzewski trial indicate large variations in the children's response to the interventions.

In general, no indication to produce a new systematic review and / or meta-analysis on RCTs comparing the effectiveness of CIMT with BIT is indicated. The large amount of different measurement instruments used in the primary trials, and the variations in the dosing of the intervention make conduction of meta-analysis inappropriate. Essential for making the evidence from quantitative research to be better accessible and understandable for clinicians is improving the quality of reporting in the research publications. Many trials base their analyses and conclusions of the differences between the groups on p-values. Where as p-values indicate the statistical significance of the findings, meaning the probability that the finding was due to chance, they do not report the size of the effect, or clinical importance of

the effect. Reporting the research findings reported with raw data would allow for objective interpretation of the findings. Calculating effect sizes would provide the reader with information about the size and direction of the effect of the interventions. So that the effect sizes are correctly interpreted, a clear indication of whether the calculations were based on the baseline to follow-up differences or on the difference between the groups at each follow-up points must be given.

For the findings in any future research to be valid and meaningful, the most robust measurement instruments that reflect the nature and goals of CIMT and BIT must be used. When the aim of the intervention is to alleviate developmental disregard, inclusion of instruments measuring performance and capacity must be considered. Qualitative studies may be used to improve the state of evidence about the personal and environmental factors that may influencing the children's response to the interventions. Similarly, qualitative studies may be used to gain deeper understanding of the meaning of improved manual ability for children with unilateral CP, and thus be essential in directing decisions of what the aim of the UE training should be for the individual child. Combining two or more data sources or methods in one trial may be used to inform different aspects of practice, and to increase the credibility of a study. The use of mixed methods would help generate evidence for physiotherapy practice that help us better understand the complex, dynamic relationships between the physical and psychosocial factors that influence human functioning (Greenfield, Greene, & Johanson, 2007; Rauscher & Greenfield, 2009).

6. Conclusion

Based on the findings in the RCTs included in this systematic review, it is not possible to confidently say that CIMT or BIT is more effective than the other in improving manual ability, participation and individual goals in children with unilateral CP at group-level. The mean group pre-post change scores exceeded a known minimal detectible change (MDC) in both groups only when attainment of individualised scores was measured with the COPM. The measurement instruments used assessed items across the ICF-CY domains, making it not possible to comprehensively report the findings using the ICF-CY, or to conduct analyses of possible interlinkages between the domains.

The finding of no to minimal difference in the effectiveness between CIMT and BIT give no clear practical advice as to which intervention on average is more effective in children with unilateral CP. Decisions about which intervention to choose for training of upper extremity function in each individual child with unilateral CP should be made in light of these findings and the findings in other research concerning CIMT and BIT. In line with the definition of evidence-based practice, the evidence from quantitative and qualitative research should be considered together with the preferences of the child and his or her family, as well as the expertise and practice knowledge of the involved therapist(s).

7. Supplementary material

The following material is included to supply the methods, findings and reasoning in this thesis.

I. Search strategy for each database
II. References for qualitative studies
III. List of publications from the research groups
IV. Reasoning for quality of conduct scoring

Supplementary material I - Search strategy for each database

OVID MEDLINE & PsycINFO

1. Cerebral Palsy/
2. cerebral pals*.mp.
3. Hemiplegia/
4. hemipleg*.mp.
5. 1 OR 2 OR 3 OR 4
6. (constraint adj3 therap*).mp.
7. CIMT.mp.
8. CI therap*.mp.
9. unimanual.mp.
10. Restraint, Physical/
11. 6 OR 7 OR 8 OR 9 OR 10
12. HABIT.mp.
13. BIT.mp.
14. bimanual.mp.
15. 12 OR 13 OR 14
16. 5 AND (11 OR 15)

EMBASE

1. Cerebral Palsy/
2. cerebral pals*.mp.
3. Hemiplegia/
4. hemipleg*.mp.
5. 1 OR 2 OR 3 OR 4
6. (constraint adj3 therap*).mp.
7. CIMT.mp.
8. CI therap*.mp.
9. unimanual.mp.
10. 6 OR 7 OR 8 OR 9

11. HABIT.mp.
12. BIT.mp.
13. bimanual.mp.
14. 12 OR 13 OR 14
15. 5 AND (11 OR 15)

CINAHL

1. MH Cerebral Palsy
2. cerebral pals*
3. MH Hemiplegia
4. hemipleg*
5. 1 OR 2 OR 3 OR 4
6. constraint N3 therap*
7. CIMT
8. CI therap*
9. unimanual
10. MH Restraint, Physical
11. 6 OR 7 OR 8 OR 9 OR 10
12. HABIT
13. BIT
14. bimanual
15. 12 OR 13 OR 14
16. 5 AND (11 OR 15)

Cochrane Library

#1 MeSH descriptor: [Cerebral Palsy] this term only

#2 cerebral pals*

#3 MeSH descriptor: [Hemiplegia] this term only

#4 hemipleg*

#5 #1 or #2 or #3 or #4

#6 Constraint adj3 therap*

#7 CIMT

#8 CI therap*

#9 MeSH descriptor: [Restraint, Physical] this term only

#10 unimanual

#11 #6 or #7 or #8 or #9 or #10

#12 BIT

#13 bimanual

#14 HABIT

#15 #12 or #13 or #14

#16 #11 or #15

#17 #5 and #16

Pubmed

1. Cerebral Palsy[MeSH Terms]

2. cerebral pals*.mp.

3. Hemiplegia[MeSH Terms]

4. hemipleg*.mp.

5. 1 OR 2 OR 3 OR 4

6. (constraint therap*).mp.

7. CIMT.mp.

8. CI therap*.mp.

9. unimanual.mp.

10. Restraint, Physical[MeSH Terms]

11. 6 OR 7 OR 8 OR 9 OR 10

12. HABIT.mp.

13. BIT.mp.

14. bimanual.mp.

15. 12 OR 13 OR 14

16. 5 AND (11 OR 15)

Supplementary material II - References to for qualitative studies

The following references to qualitative studies conducted on the theme of the thesis were found:

- Nordstrand et al. (2013) Six years after a modified constraint induced movement therapy (CIMT) program--what happens when the children have become young adults?
- Gilmore et al. (2010) A balancing act: children's experience of modified constraint-induced movement therapy
- Rosa-Rizzotto et al. (2010) The perception of involved professionals towards research feasibility and usefulness: Lessons from the multi-site trial on efficacy of constraint induced movement therapy in children with hemiplegia
- Skold et al. (2004) Performing bimanual activities: the experiences of young persons with hemiplegic cerebral palsy.

Supplementary material III - Excluded publications from the research groups

The research groups conducting trials about CIMT and BIT have published multiple articles concerning the same trial, with focus on different outcome measures and / or different follow-up points. A full list of the publications to date is provided below.

Sakzewski (INCITE)

- Two articles on the results at 52 weeks follow-up; one on the primary outcome measures (AHA, MUUL, COPM) (Sakzewski, Ziviani, et al., 2011a), and one on the quality of life measures (CPQOL-Child, KIDSCREEN-52) (Sakzewski et al., 2012).
- Two articles on the results at 26 weeks follow-up; one on the participation outcomes (COPM, PEDI, LIFE-H) (Sakzewski, Ziviani, et al., 2011b), and one on the activity outcomes (AHA, MUUL) (Sakzewski, Ziviani, et al., 2011c).
- An article on the analysis of the best responders to CIMT and BIT (Sakzewski, Ziviani, & Boyd, 2011).
- An article on the trial methodology (Boyd et al., 2010).

Gordon 2011

- Results concerning all 42 children participating in the trial were reported in one article (Gordon et al., 2011).
- Hung et al. (2011) used the first 20 participants to assess the effect of CIMT and BIT on bimanual coordination measured with 3D kinematics.
- de Brito Brandao et al. (2012) used the last 16 participants to assess the effect of CIMT and BIT on daily functioning measured with the PEDI and the COPM.

Fedrizzi 2013

- An article on the immediate post-intervention results (Facchin et al., 2011).
- An article on the results at six months follow-up (Fedrizzi, Rosa-Rizzotto, Turconi, Pagliano, Fazzi, Pozza, & Facchin, 2013).
- An article on trial methodology (Facchin et al., 2009).

Supplementary material IV - Reasoning for scoring of the quality of conduct questions

The following tables provide specific reasoning for scoring of the quality of conduct questions for each trial. Page numbers and paragraphs (R = right, L = left) in the articles relevant to the answers are given. In questions consisting of two parts, the reason for an overall answer of 'no' is indicated as bold text.

For question 3, table 2 in this thesis (Measurement instruments included) was used to assist in scoring of the description, validity and reliability of the measurement instruments. It should be noted that question 5 about power calculations asks whether or not any power calculations were conduced; it does not require that enough participants were recruited so that the trial would have adequate power. As discussed in the methods chapter under 'Assessment of quality of conduct', question 7 "Considering the potential within the study design, were appropriate methods for controlling confounding variables and limiting potential biases used?" was answered based on the study's ability to limit four sources of systematic bias defined in the Cochrane Handbook for systematic reviews (Higgins & Green, 2011, p. 80).

Fedrizzi et al. 2013

1. Were inclusion and exclusion criteria of the study population well described and followed?	
Yes	- Clear inclusion & exclusion criteria, p.162, R - Followed: table 1
2. Was the intervention well described and was there adherence to the intervention assignment? For 2-group designs, was the control exposure also well described? ***(Both parts of the question need to be met to score 'yes'.)***	
No	- Description: yes, p. 163 - **Adherence: not described or reported** [Parents were asked to fill in a questionnaire about treatment compliance (ad hoc questionnaire), however, the results were not presented in the current article, p. 164.]

3. Were the measures used clearly described, valid and reliable for measuring the outcomes of interest?	
No	- Primary measurement instruments: Besta scale, QUEST - Description, validity & reliability **Besta scale:** information on validity, ICF categories and responsiveness missing **(table 2).** - Description, validity & reliability **QUEST:** variable inter- & intrarater reliability **(table 2)**
4. Was the outcome assessor unaware of the intervention status of the participants (i.e., were the assessors masked)?	
Yes	- 2 blinded supervisors evaluating patients, p. 163, L, 4th paragraph
5. Did the authors conduct and report appropriate statistical evaluation including power calculations? *(Both parts of the question need to be met to score 'yes'.)*	
Yes	- Conduct of statistical evaluation: yes p. 164, R; p. 165, L - Reporting: yes (mean + SD reported for each group at each follow-up in a table; change scores reported in tables; in writing only p-values reported, no other output from statistical tests) - Power calculations: yes p. 162, R, bottom of the page. [According to power calculations 111 participants needed; 105 were recruited (p. 165, L).]
6. Were dropout / loss to follow-up reported and less than 20%? For 2-group designs, was dropout balanced?	
Yes	- Drop-out rate in CIMT group 0% and in BIT group 10% p. 165, R, 1st paragraph, (however this left the groups with CIMT n=39, BIT n=30)
7. Considering the potential within the study design, were appropriate methods for controlling confounding variables and limiting potential biases used?	
No	- Study design: multicenter, cluster RCT - Allocation was concealed up to the start of the intervention **- No reporting of whether the interventions were carried out as intended, or if co-interventions were avoided (possible performance bias)** - Loss of participants similar in both groups - Outcome assessors were blinded
Total score: 4 / 7 (moderate)	

Sakzewski et al. 2011 (INCITE)

1. Were inclusion and exclusion criteria of the study population well described and followed?	
Yes	- Clear inclusion & exclusion criteria, p. 665, L - Followed: fig 1. trial profile, p. 667

2. Was the intervention well described and was there adherence to the intervention assignment? For 2-group designs, was the control exposure also well described? ***(Both parts of the question need to be met to score 'yes'.)***	
No	- Description: yes, p. 665, R - **Adherence: not reported.** [6 children (CIMT n=4, BIM n=2) received Botox injections in the UL and concurrent therapy between weeks 26 and 52 as part of their standard care p. 666, R, 2nd paragraph.]
3. Were the measures used clearly described, valid and reliable for measuring the outcomes of interest?	
Yes	- Primary measurement instruments: AHA, MUUL; secondary: JTTHF, COPM, LIFE-H - Description, validity & reliability AHA, MUUL, COPM, LIFE-H yes, p. 665-666, table 2 - Description, validity & reliability JTTHF: lack of evidence of validity & reliability, table 2
4. Was the outcome assessor unaware of the intervention status of the participants (i.e., were the assessors masked)?	
No	- **All assessments performed by non-blinded OTs & PTs**; AHA and MUUL were videotaped and scored by blinded OTs, p. 666, L, 1st paragraph
5. Did the authors conduct and report appropriate statistical evaluation including power calculations? *Both parts of the question need to be met to score 'yes'.*	
Yes	- Statistical evaluation: yes, p. 666. - Power calculations: yes, p. 665, R, 2nd paragraph. (According to power calculations 52 participants needed; 54 were recruited)
6. Were dropout / loss to follow-up reported and less than 20%? For 2-group designs, was dropout balanced?	
Yes	- 92% retained at 12 months (n=2 CIMT; n=3 BIM lost), p. 666, R, 2nd paragraph
7. Considering the potential within the study design, were appropriate methods for controlling confounding variables and limiting potential biases used?	
No	- Study design: Matched-pairs RCT - Allocation was concealed up to the start of the intervention **- No reporting of whether the interventions were carried out as intended, or if co-interventions were avoided (6 children out of 54 received co-interventions during follow-up period) (possible performance bias)** - Drop-out rate similar in both groups **- Persons performing assessments were not blinded (possible detection bias)**
Total score: 4 / 7 (moderate)	

Sakzewski et al. 2012 (INCITE, quality of life measures)

1. Were inclusion and exclusion criteria of the study population well described and followed?	
Yes	- Clear inclusion & exclusion criteria, p. 416, L, 3rd paragraph - Followed: fig 'Trial profile' 1, p. 418 + table 1 p. 419
2. Was the intervention well described and was there adherence to the intervention assignment? For 2-group designs, was the control exposure also well described? ***(Both parts of the question need to be met to score 'yes'.)***	
No	- Description: yes, p. 416, L paragraph **- Adherence: not reported**
3. Were the measures used clearly described, valid and reliable for measuring the outcomes of interest?	
Yes	- Primary measurement instrument: CPQOL; secondary measurement instrument: KIDSCREEN-52 - Description, validity & reliability CPQOL: yes, p. 416, R, 2nd paragraph; table 2 - Description, validity & reliability KIDSCREEN-52: yes, p. 417, L, 1st paragraph; table 2
4. Was the outcome assessor unaware of the intervention status of the participants (i.e., were the assessors masked)?	
No	- Measures completed by children and / or families before each follow-up assessment, p. 417, L, 2nd paragraph
5. Did the authors conduct and report appropriate statistical evaluation including power calculations? *Both parts of the question need to be met to score 'yes'.*	
Yes	- Statistical evaluation: yes, p. 417, 3rd paragraph - Power calculations: p. 416, L, last paragraph. *(According to power calculations 72 participants needed; 54 were recruited.)*
6. Were dropout / loss to follow-up reported and less than 20%? For 2-group designs, was dropout balanced?	
Yes	- Total 11% lost to follow-up (CIMT n=2/32 = 6.25%; BIM n = 4/32 = 12.5%), p. 418, fig 1 trial profile
7. Considering the potential within the study design, were appropriate methods for controlling confounding variables and limiting potential biases used?	
No	- Study design: matched-pairs RCT - Allocation was concealed up to the start of the intervention - **No reporting of whether the interventions were carried out as intended, or if co-interventions were avoided (possible performance bias)** - Drop-out rate similar in both groups **- Not possible to blind outcome assessors (self/parent-reported measure) (possible detection bias)**
Total score: 4 / 7 (moderate)	

Gordon et al. 2011

1. Were inclusion and exclusion criteria of the study population well described and followed?	
Yes	- Clear inclusion & exclusion criteria, p. 693, L, 3rd paragraph - Followed: baseline participant characteristics, p. 696, fig 1.
2. Was the intervention well described and was there adherence to the intervention assignment? For 2-group designs, was the control exposure also well described? ***(Both parts of the question need to be met to score 'yes'.)***	
Yes	- Description: yes, p. 693-4 - Adherence: yes; complete adherence confirmed by direct observation by supervisors and daily logs. Home logs indicated an average of 286 min of the requested 360min / week practice during the 6 months following the intervention, p. 695, R, 1st paragraph
3. Were the measures used clearly described, valid and reliable for measuring the outcomes of interest?	
Yes	- Primary measurement instruments: AHA, JTTHF; secondary measurement instruments: QUEST, GAS, activity monitor - Description, validity & reliability AHA: yes, p. 694, L, 2nd paragraph; table 2 - Description, validity & reliability JTTHF: variable psychometric properties reported, no details of validity, p. 694, L, 3rd paragraph; table 2 - Description, validity & reliability QUEST: variable intra- and interrater reliability, p. 694, L, 4th paragraph; table 2 - Description, validity & reliability GAS: variable psychometric properties reported, p. 694, L, 5th paragraph; table 2
4. Was the outcome assessor unaware of the intervention status of the participants (i.e., were the assessors masked)?	
Yes	- p. 693, L, 1st paragraph
5. Did the authors conduct and report appropriate statistical evaluation including power calculations? *Both parts of the question need to be met to score 'yes'.*	
Yes	- Statistical evaluation: yes, p. 695 - Power calculations: yes, p. 695, L, 3rd paragraph. *(According to power calculations 41 participants needed; 42 recruited, p. 695, L, 5th paragraph.)*
6. Were dropout / loss to follow-up reported and less than 20%? For 2-group designs, was dropout balanced?	
Yes	- One dropout in each group, p. 696, fig.1
7. Considering the potential within the study design, were appropriate methods for controlling confounding variables and limiting potential biases used?	

Yes	- Research design: matched-pairs RCT - Allocation was concealed up to the start of the intervention - Interventions were carried out as intended [participants stopped usual and customary care during the treatment but resumed afterward (proportion receiving therapy was similar between groups: p>.05, Table 1). No changes to preexisting therapy. p. 695, R, 2nd paragraph] - Drop-out rate similar in both groups - Outcome assessors were blinded
Total score: 7 / 7 (strong)	

de Brito Brandao et al. 2012

1. Were inclusion and exclusion criteria of the study population well described and followed?	
No	- Inclusion criteria **(lacks specificity)**, p. 673, R. **Exclusion criteria not reported.** - **Followed: not completely reported** (in table 1 only limited info on participants, no study flow graph provided)
2. Was the intervention well described and was there adherence to the intervention assignment? For 2-group designs, was the control exposure also well described? ***(Both parts of the question need to be met to score 'yes'.)***	
No	- Description: yes, p. 674-5 **- Adherence: not reported**
3. Were the measures used clearly described, valid and reliable for measuring the outcomes of interest?	
Yes	- Measurement instruments: COPM, PEDI (only the self-care functional skills section and the caregiver assistance section, p. 674, L) - Description, validity & reliability COPM: yes, p.674, L, 2nd paragraph; table 2 - Description, validity & reliability PEDI: yes, p. 674, R, 1st paragraph; table 2 *(information on psychometric properties available when the whole test is used; not when subtests are used independently)*
4. Was the outcome assessor unaware of the intervention status of the participants (i.e., were the assessors masked)?	
No	- The first author conducted the interviews for the PEDI and the COPM, p. 675, R, 3rd paragraph
5. Did the authors conduct and report appropriate statistical evaluation including power calculations? *Both parts of the question need to be met to score 'yes'.*	
No	- Statistical evaluation: yes, p. 675, R, 4th paragraph - p. 676, L **- Power calculation: not reported**

6. Were dropout / loss to follow-up reported and less than 20%? For 2-group designs, was dropout balanced?	
Yes	- The dropout rate was not reported, but it can be inferred from table 2, p. 677, that all participants completed the study
7. Considering the potential within the study design, were appropriate methods for controlling confounding variables and limiting potential biases used?	
No	- Research design: RCT - **Allocation was not concealed up to the start of the intervention (possible selection bias)** *["From a practical standpoint, concealing allocation up to the point of assignment is always possible, regardless of the study question"* (Higgins & Green, 2011, p. 81)*]* - **No reporting of whether the interventions were carried out as intended, or if co-interventions were avoided (possible performance bias)** - Drop-out rate similar in both groups - **Outcome assessor was not blinded (possible detection bias)**
Total score: 2 / 7 (weak)	

Hung et al. 2012

1. Were inclusion and exclusion criteria of the study population well described and followed?	
No	- Description: inclusion criteria described, p. 2725, 2.1. **Exclusion criteria not described**. - **Followed: not reported** (no study flow graph provided)
2. Was the intervention well described and was there adherence to the intervention assignment? For 2-group designs, was the control exposure also well described? ***(Both parts of the question need to be met to score 'yes'.)***	
No	- Description: yes, p. 2726 - Adherence: not reported
3. Were the measures used clearly described, valid and reliable for measuring the outcomes of interest?	
No	- Measurement instruments: drawer-opening task with 3-D kinematics, AHA - Description, validity & reliability drawer-opening task (3-D kinematics): description, p. 2727; **validity & reliability not reported**; **table 2** - Description, validity & reliability AHA: **description lacking, p. 2727; validity & reliability not reported; table 2**
4. Was the outcome assessor unaware of the intervention status of the participants (i.e., were the assessors masked)?	
Yes	- Blind evaluator, p. 2726, 5th line, p. 2727, 3rd line

5. Did the authors conduct and report appropriate statistical evaluation including power calculations? *Both parts of the question need to be met to score 'yes'.*	
No	- Statistical evaluation: yes, p. 2727, 3rd paragraph **- Power calculation: not reported**
6. Were dropout / loss to follow-up reported and less than 20%? For 2-group designs, was dropout balanced?	
No	- Drop-out rate not reported
7. Considering the potential within the study design, were appropriate methods for controlling confounding variables and limiting potential biases used?	
No	- Research design: RCT - **Not reported whether allocation was concealed up to the start of the intervention (possible selection bias)** - **Not reported whether the interventions were carried out as intended or if co-interventions were avoided (possible performance bias)** - Drop-out rate not reported and cannot be inferred from the data (attrition bias) - Blinded outcome assessor
Total score: 1 / 7 (weak)	

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