A RANDOMISED CONTROLLED TRIAL AND SYSTEMATIC REVIEW COMPARING TWO METHODS OF CONSTRAINT INDUCED MOVEMENT THERAPY TO IMPROVE UPPER LIMB FUNCTION IN PRE-SCHOOL CHILDREN WITH HEMIPLEGIC CEREBRAL PALSY

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Abstract

Constraint induced movement therapy (CIMT) which is supported by motor learning theory has demonstrated promising results in improving upper limb function in hemiplegic cerebral palsy (HCP). However, its effectiveness within the NHS where children in the UK usually receive their therapy is little understood.

To provide clarification, the author conducted a randomised controlled trial (n = 62) in 16 NHS paediatric community therapy services which compared the feasibility and effectiveness of a novel approach (prolonged restraint) of CIMT with usual NHS practice, in the young child with HCP. The primary outcome was bimanual performance measured with the Assisting Hand Assessment (AHA).

Immediately post-intervention both groups changed and although there was not a statistically significant group difference the prolonged restraint methodology resulted in a larger effect (0.5 versus 0.2). The novel approach was safe, feasible, and acceptable to families and a more effective method of treatment delivery. The trial findings were combined in a systematic review and meta-analysis with a similar study and a treatment effect of 0.92 AHA logits was demonstrated. This is compatible with the smallest detectable difference (0.97 logits) indicating actual change in bimanual performance.

The short-term efficacy, excellent recruitment and retention rates and acceptability of the trial procedures provides support for the trial feasibility and the need for a definitive investigation.

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List of abbreviations

AA	Dr Anne Aukett
AHA	Assisting Hand Assessment
AW	Andrew Walker
BBMQ	Birmingham Bimanual Questionnaire
BTX-A	Botulinum toxin type A
CATCH	Randomised controlled trial comparing two methods of constraint induced movement therapy to improve upper limb function in pre-school children with hemiplegic cerebral palsy
CCT	Clinical controlled trial
CI	Confidence interval
CIMT	Constraint induced movement therapy
CP	Cerebral palsy
CRB	Criminal Records Bureau
GCP	Good Clinical Practice
HABIT	Hand arm bimanual intensive therapy
HCP	Hemiplegic cerebral palsy
HRQOL	Health related quality of life
ICC	Interclass correlation
ICF	International Classification of Functioning, Disability and Health
JM	Julie Markell (Patients, public involvement representative)
MF	Dr Max Feltham
NICE	National Institute For Health and Care Excellence
NDT	Neurodevelopmental therapy
NHS	National Health Service

OR	Odds ratio
PALS	Patient Advisory Liaison Service
PC	Pauline Christmas
PC-CRTU	Primary Care-Clinical Research and Trials Unit t
PDMS-2	Peabody Developmental Motor Scales
PedsQL	Paediatric quality of life
PMAL-R	Paediatric Motor Activity Log-Revised
QUEST	Quality Of Upper Extremity Skills Test
R&D	Research and Development
RCT	Randomised controlled trial
SCPE	Surveillance of Cerebral Palsy in Europe
SEM	Standard error of the mean
SMD	Standardised mean difference
TH	Dr Tom Hoppitt
TSDMC	Trial Steering and Data Monitoring Committee
UKCP	United Kingdom Cerebral Palsy
UoB	University of Birmingham
WEE-FIM	Functional Independence Measure for Children
WHO	World Health Organisation
WMFT	Wolf Motor Function Test

Chapter 1: Setting the scene. Hemiplegic cerebral palsy

1.1. Introduction

Cerebral palsy (CP) is a group of motor disorders which begin in infancy and persist for a lifetime causing a range of permanent disabilities. Children with CP have difficulty achieving independence and participating in society and often require long-term support from their families. There is frequently a need for lifelong interventions from healthcare services. This thesis focuses on hemiplegic cerebral palsy (HCP) which is characterised by unilateral motor impairment and affects approximately one third of children with CP in the UK (Surman et al., 2006). Children with HCP usually have the intellectual capacity to attend main stream education, but impaired arm function in particular can restrict their participation in society.

Beecham et al. (2001) estimated that in the previous year the health and social care costs of 81 young adults (16-24 years) with HCP in the UK, was just over one million pounds. Forty-three percent related directly to the HCP impairments. Greater use was made of the NHS compared to the general population (e.g., 35% compared to 16% had a specialist doctor consultation and 12% versus 4% received physiotherapy). In terms of participation the proportion of young adults working for a higher degree was similar to the general population. However, considerably more

were unemployed (20% versus 8%), more unmarried/not cohabiting (88% compared to 52%) and most (73%) continued to live with their parents (Beecham et al., 2001).

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Physiotherapists and occupational therapists have traditionally provided rehabilitation interventions within the NHS for children with HCP. A broad range of interventions are available for the upper limb including occupational therapy (Case-Smith, 1995; 1996; 2000), neurodevelopmental therapy (Fetters and Kluisick, 1996; Brown and Burns, 2001), conductive education (Reddihough et al., 1998) and peripheral splinting and casting (Blair et al., 1996; Law et al., 1997). Furthermore, adjuncts may be administered alongside the therapy including intramuscular injections of botulinum toxin type A (Corry et al., 1997; Fehlings et al., 2001; Reeuwijk et al., 2006). However, therapeutic management of the upper limb can be both resource-intensive and costly as well as needing a heavy time commitment from the therapist and the children and their families. Despite the financial and time commitments the effects of different upper limb treatments are not well understood or evidenced (Boyd et al., 2001; Sakzewski et al., 2009).

Constraint induced movement therapy (CIMT) is an approach developed from neuroscience (Taub, 1980) for individuals with a unilateral motor impairment and has shown positive results in the adult stroke population (Sirtori et al., 2009). Furthermore, it has demonstrated promising results worthy of further investigation in HCP (Hoare et al., 2007). This chapter will include the relevant background literature to inform an investigation of CIMT in the HCP population. An overview of the movement disorder of CP and its subgroup HCP will be included. Furthermore, a

summary of the impairments and activity limitations of the upper limb in HCP and the current rehabilitation interventions offered by therapists to ameliorate these symptoms will be discussed. The reasons for conducting research to evaluate the efficacy of CIMT for the upper limb in HCP will be outlined.

1.2. Cerebral palsy

1.2.1. Definition

Cerebral palsy (CP) is a well-known term amongst health professionals and members of the public, which refers to a group of neurodevelopmental disorders. However, the definition of CP has been somewhat of a challenge to capture. There have been a number of attempts to define the condition. Primarily to enable measurement of the disease, evaluate its impact and to offer suitable health management strategies including development of appropriate treatment interventions. An early definition by an international working group of eminent clinicians reported and annotated by Bax (1964), and still frequently cited defines CP as:

"*a disorder of movement and posture due to a defect or lesion of the immature brain"* (Bax, 1964, p.295).

It was considered by the working group that this simple definition may be readily translated and therefore, universally accepted. However, it was considered unsatisfactory as it focused exclusively on motor aspects. Furthermore, it did not explicitly identify exclusion criteria for individuals who presented with the recognised

phenotype, but with progressive or short term disease (Rosenbaum et al., 2007). Since then there have been a number of attempts to refine the definition. Indeed, in a collaborative network of European CP registers and surveys (i.e., Surveillance of Cerebral Palsy in Europe; SCPE) a total of five different definitions were used across 14 European centres (Cans, 2000). Eight centres used the definition above (Bax, 1964), three others used a definition compiled by Mutch et al. (1992) and the three remaining used other definitions (Ingram, 1984; Mac Keith et al., 1959). In order to allow standardisation of data collection internationally, the collaboration decided that participating centres should continue with their choice of definition providing that it included five key elements. These are that CP:

- is a group of disorders;
- is permanent but not unchanging;
- involves a disorder of movement and/or posture and of motor function;
- is due to a non-progressive lesion;
- originates in the immature brain (Cans, 2000).

A number of CP registers have adhered to these inclusion criteria, including the United Kingdom CP database (UKCP) which has pooled data from five UK registers (Merseyside and Cheshire, North of England, Northern Ireland, Oxford and Scotland) for birth years 1960-1997(Surman et al., 2006).

Recently an international group of clinical and scientific experts have convened to revisit the definition and classification of CP. Primarily in relation to the emerging need to evaluate the status of information about CP. This has been prompted by a

number of factors including an acknowledgement that this developmental motor impairment is almost invariably associated with a range of other neurodevelopmental disabilities and a change in concept about function and disability (Rosenbaum et al., 2007). They defined CP as:

> *"a group of permanent disorders of the development of movement and posture, causing activity limitations that are attributed to non-progressive disturbances that occurred in the developing foetal or infant brain. The motor disorders of CP are often accompanied by disturbances of sensation, perception, cognition, communication and behaviour, by epilepsy and by secondary musculoskeletal problems"*
> (Rosenbaum et al., 2007, p.9).

This definition of CP will be used as the working definition in this thesis. It incorporated the five key points established by the SCPE (Cans, 2000) and thus fulfils the inclusion criteria for both the European and the more recent UKCP database (Surman et al., 2006).

A key addition to this definition was the use of an updated model, the International Classification of Functioning, Disability and Health (ICF, World Health Organisation, 2001) to describe the condition. This classification system has been endorsed by all 191 WHO member states in the 54th World Health Assembly (resolution WHA 54.21; 2001) as the international standard to describe and measure health and disability. The ICF classifies a disorder using a multilevel approach in terms of the effect it has

on an individual using clearly defined health domains. This includes the effect on the bodily structures and functions (anatomical body parts and physiological bodily functions), on the individual's activity (task execution) and their societal participation in life situations (World Health Organisation, 2002). In addition, this multilevel approach can be administered to clearly distinguish interventions administered to improve functioning and ameliorate disability and code outcomes in light of the aspect of disability that the intervention intends to address (World health organisation, 2013).

The use of the ICF to define CP provided detail of the level at which the condition affects the individual. It clarified that the disorders of posture and movement are substantial enough to lead to activity limitation. Furthermore, it has provided guidance on appropriate interventions for amelioration of the condition and suitable outcome measures to evaluate their success. Therefore, in the CATCH trial it has provided guidance on the requirements for the interventions (i.e., needs to ameliorate at the activity level) under investigation but also on the outcome measures to evaluate efficacy. Despite the usefulness of the influence of the ICF framework on the CP definition, provided by Rosenbaum and colleagues (2007), it also is open to criticism. This is primarily because it omits a reference to societal participation, which can also be the focus of therapy but is beyond the scope of this thesis.

1.2.2. Classification

The characteristics used to classify CP are; topography, predominant neurological impairment and degree of disability (Rosenbaum et al., 2007). Individuals with CP

can be classified topographically into unilateral and bilateral presentations and given a diagnostic label of hemiplegic cerebral palsy (HCP) or quadriplegic cerebral palsy, respectively. However, the unilateral grouping may have limitations with evidence suggesting that impairments may not be exclusively restricted to one side (Bax et al., 2005; Steenbergen and Meulenbroek, 2006). In some instances the terms “less affected“ and “more affected” side is used. CIMT was developed for individuals with a unilateral abnormality affecting one side of the body as opposed to full body involvement. Therefore, disease topography was required to identify suitable participants in the CATCH trial. Although, the classification may have some limitations it was considered suitable to identify patients. Therefore only children classified with HCP were included.

It is recognised that CP presents with a range of neurological impairments (Rosenbaum et al., 2007). A consensus on classification of CP was developed based on the predominant neurological impairments of the body structures and functions using the European network of CP registers and population-based surveys (Cans, 2000). Observed abnormalities include hypertonus (increased muscle tone), hypotonus (decreased muscle tone) and abnormal patterns of posture and movement. These presentations are used to define CP subgroups which include; spastic, ataxic and dyskinetic (dystonic and choreo-athetotic). The presenting characteristics of each subgroup are outlined in Table 1.1.

Table 1.1. Characteristics of cerebral palsy subgroups

Classifications	Characteristics
Spastic	Abnormal pattern of posture and/or movement Hypertonus (Increased muscle tone velocity dependent, not necessarily constant) Pathological reflexes (increased reflexes: hyperreflexia)
Ataxia	Abnormal pattern of posture and/or movement Hypotonus Loss of orderly muscular coordination so that movements are performed with abnormal force, rhythm, and accuracy
Dyskinetic	Abnormal pattern of posture and/or movement Involuntary, uncontrolled, recurring, occasionally stereotyped movements
Dystonic	Hypokinesia (reduced activity, i.e. stiff movement) Hypertonia (tone usually increased)
Choreo-athetotic	Hyperkinesia (increased activity, i.e. stormy movement) Hypotonia (tone usually decreased)

(Adapted from Cans, 2000, p.821)

Children classified with spasticity present most commonly. Indeed, the SCPE found that of the 4792 children with CP (1980-1990), 85.7% were classified with spasticity, compared to 6.5% with dyskinesia, 4.3% with ataxia, and the remaining 3.7% were unclassified (Johnson, 2002). However, it has been recognised that there can be difficulties with classification according to the predominant neurological impairment because of mixed neurological symptoms and therefore difficulty with differentiation into a specific group. CIMT has not been developed as a treatment intervention for individuals with a specific neurological impairment. Therefore, participants with the complete range of neurological presentations were included in the CATCH trial.

The degree of motor disability in CP can vary considerably from a mild motor issue that can be difficult to recognise to total dependence for activities of daily living. This has traditionally been subjectively categorised as mild, moderate, or severe but these classifications have never been operationally defined (Johnson, 2002). Although more recently functional assessments have been administered, which are more likely to provide a comprehensive assessment of degree of motor disability. Uvebrant (1988) in a population based study (n=169) classified upper limb disability in HCP with eight different types of grips including pinch and tripod (Sollerman, 1980; cited in Ubervant, 1980, p. 56). Items were scored as; one for a completed grip, two when completed with difficulty and three when not completed. Scores ranged from 8-24. Nearly half (47%) were classified as mild (scored < 12), 39% as moderate (scored 12-20), and 14% as severe (scored 20). CIMT has not been developed for a specific

level of motor disability consequently, children with the full range of disability were included in the CATCH investigation.

1.2.3. Prevalence

In order to understand the scale of the problem investigated within the CATCH trial it is important to be aware of the numbers of children affected by the HCP condition. The intervention under investigation was developed to be suitable for an NHS environment, therefore of particular relevance is the numbers affected within the UK. CP is thought to be the most common cause of physical disability in early childhood but the proportion of children in the population affected is relatively small (Surveillance of Cerebral Palsy in Europe, 2000). UK wide data on CP is not collected routinely. However, Surman et al. (2006) combined five active UK based CP registers. The pooled data has to be viewed with caution because of local inconsistencies, but this is currently the only means of describing a UK wide picture. They found the mean annual prevalence rates of CP in the UK (1976-1996) peaked in the 1980's and then plateaued and was generally lower in the 1990s (shown in Figure 1.1). In the UK the mean prevalence of CP was 2.0 per 1000 live births for years 1986-1996 (Surman et al., 2006). This was similar to the findings from the Surveillance of Cerebral palsy in Europe (SCPE), which included 14 centres in eight countries. They found the prevalence rate to be 2.08 per 1000 for the 1980-1990 birth years (Johnson, 2002).

The National Institute for Health and Care Excellence guidelines on Spasticity in children and young people with non-progressive brain disorders (2012) reported that a total of 110,000 people in the UK had cerebral palsy. However, this was based on figures provided from the Neurological Alliance, Neuro Numbers: A brief review of the numbers of people in the UK with a neurological condition published in 2003 and therefore, is probably an underestimation. Although definitive figures of the number of children with CP is unclear, it is considered the most common cause of physical difficulty in children (Surveillance of Cerebral Palsy in Europe, 2000) and an effective intervention for the upper limb would be of benefit.

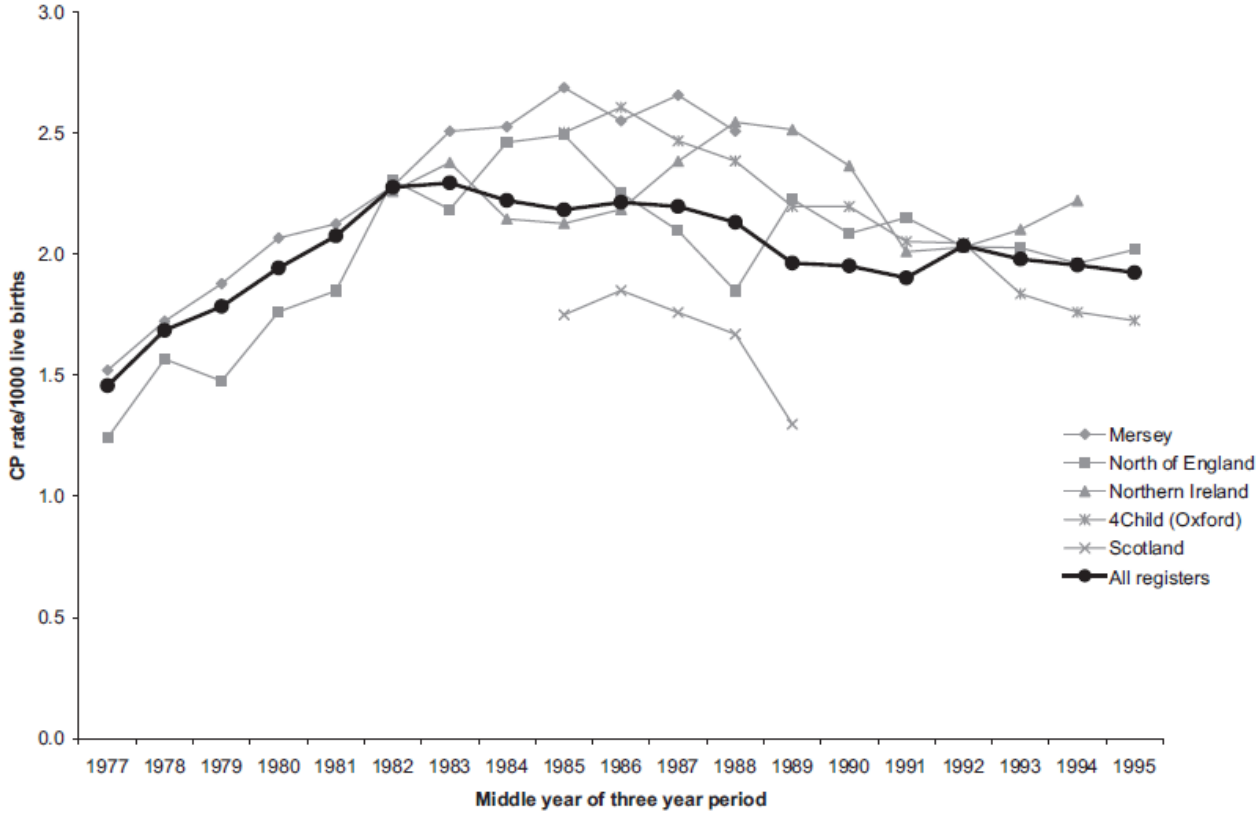


Figure 1.1. Rate of cerebral palsy per 1000 live births for the UKCP database and individual registers

(Surman et al., 2006, p. 153) Printed with permission

1.2.4. Aetiology

The brain insult leading to CP can be categorised as damage, malformation or disorders of function of the brain, which are not mutually exclusive. The cause of the insult can be considered as a sequence of causal factors leading to an event in the developing brain (Eunson, 2012). However, the complete causal pathways of CP are not well understood (Eunson, 2012). Amongst the most common risk factors are prematurity and low birthweight. Indeed prevalence of CP has been reported as inversely associated with gestational age and birth weight. Ninety cases per 1000 live births are reported in babies with a birth weight of 1000g compared to 1.5 cases per 1000 live births for babies weighing at least 2500g (National Institute For Health and Care Excellence guidelines, 2014). The insult occurs either during the foetal period or after birth with no explicit upper age limit (it is agreed that the first two or three years have the most impact on motor function; Rosenbaum et al., 2007). Therefore, children with HCP as a result of brain injury which occurred either pre-birth or post-birth with no upper age limit were included in the CATCH trial.

A key development in the management of CP has been the evaluation of brain structure with magnetic resonance imaging (MRI) to establish aetiology (Ashwal et al., 2004). Indeed, in a systematic review on the role of MRI in elucidating the aetiology of CP, abnormality was found in 334 of 388 (86%) of CP patients and gave indications to pathogenesis in 83% of cases (Krageloh-Mann and Horber, 2007). Although, neuroimaging, plays a role in determining causation of the condition and is of increasing importance to diagnosis of CP (Ashwal et al., 2004), a definitive

diagnosis continues to rely on clinical assessment conducted usually by a specialist doctor (O.'Shea, 2008). This informed the eligibility process in the CATCH trial reported in the thesis. Only children who had a confirmed diagnosis of HCP following a medical assessment were included.

1.3. Hemiplegic cerebral palsy

Approximately a third of children born with CP in Europe (1980-1990) had a unilateral disability (Johnson, 2002) which is similar to the UK (1960-1997) only registers (Surman et al., 2006). The predominant cause of the damage, malformation or disorders of function of the brain leading to HCP is a focal lesion of the brain usually as a result of a perinatal stroke. Although this is a well-recognised condition, there are a number of aspects that remain elusive. To address some of these issues the National Institute of Child Health and Human Development and the National Institute of Neurological Disorders and Stroke convened a workshop of leading experts. They defined perinatal stroke as:

> "*a group of heterogeneous disorders in which there is a focal disruption of cerebral blood flow secondary to arterial or venous thrombosis or embolization between 20 weeks of foetal life through to the 28th post-natal day and confirmed by neuroimaging or neuropathological studies*" (Raju et al., 2007, p.610).

A number of distinct perinatal stroke syndromes are characterised by a focal infarction in the cortical and / or, subcortical area within an otherwise healthy brain. The distinction between subgroups depends on when the insult occurred (before or near birth), the mechanism (ischemic or haemorrhagic; arterial or venous), and if the child became symptomatic as a new born or during infancy (Kirton and deVeber, 2013). Risk factors for perinatal stroke have been identified including; neonatal factors (e.g., infection, perinatal asphyxia), maternal factors (pre-eclampsia, infection and birth complications) and miscellaneous factors including dehydration and ethnicity (Raju et al., 2007). Lee et al. (2005) conducted a population-based (USA), case-controlled study (1997-2002) that included 199,176 infants. They identified significant maternal risks for perinatal stroke that included pre-eclampsia with an odds ratio (OR) of 5.3 and 95% confidence interval (CI) 1.3 to 22.0 and prolonged rupture of membranes, OR, 3.8, 95% CI: 1.1 to 12.8. However, the presence of risk factors in both the mother and the infant has been described as multifactorial and the interactions poorly understood (Raju et al., 2007).

Despite the focal nature of the insult HCP often presents with accompanying non-motor deficits. In their review of life after perinatal stroke, Kirton and deVeber (2013) described not only a resultant motor deficit but also a number of associated non-motor deficits. These included; cognitive, sensory, visuospatial impairment and epilepsy. For example, Wanigasinghe et al. (2010) examined a population based CP registry and found that more than 50% (34/62) of children with perinatal stroke presented with epilepsy in conjunction with HCP.

1.3.1. Upper limb impairments in HCP

The predominant impairment of the body structure and function associated with HCP is abnormal muscle tone, known as spasticity. This is reflected in the UKCP database in which all (n=2296) individuals were included in the spastic subgroup (Surman et al., 2006). In order to describe the clinical features associated with spasticity an interdisciplinary workshop (American Task Force on Childhood Motor Disorders) including neurologists, paediatricians and therapists was established (Sanger et al., 2003). They described spasticity as abnormally increased muscle tone causing excessive resistance that changes with speed (velocity dependent) and direction within a muscle. Furthermore, the resistance increases rapidly beyond a threshold speed or joint angle at which point a "spastic catch" or clonus may be felt (Sanger et al., 2003). The definition has been adopted by NICE (2012) guidelines on spasticity for children and young adults.

The taskforce suggested that it was likely many children with a primarily spastic presentation will also have some degree of dystonia (i.e., involuntary and uncontrolled movements) and this is commonly seen in the upper limb in HCP (Sanger et al., 2003). The probable existence of a combination of motor impairments is a shift away from the traditional view which considered spasticity may present with hyperreflexia, weakness and clonus but that dystonia, was a different type of impairment resulting from damage in a different location of the brain. These motor presentations were not expected to occur simultaneously. However, it was recognised that a lesion which occurs in one motor system can have secondary effects on the function of other motor pathways leading to a mixed clinical

presentation (Sanger et al., 2003). NICE guidelines (2012) on spasticity for children and young adults have recognised the importance of this mixed presentation. They describe spasticity as one component which co-exists with other motor symptoms which includes dystonia. Therefore, when considering the clinical impairment in HCP spasticity leading to velocity dependent hypertonia, hyperreflexia, clonus and weakness in conjunction with associated motor disorders such as dystonia may be present.

Mirror movements are voluntary movement of one hand associated with unintended movements of the contralateral hand (Woods and Teuber, 1978) which may also hinder motor activity. Although these movements are observed in typically developing young children, they will usually be suppressed with motor development. Kuhtz-Buschbeck et al. (2000) measured mirror activity and hand function in children with HCP (n=22) compared to a typically developing group (n=17). They found mirror movement was not only more common in HCP than typically developing children (i.e., 95% in HCP versus 58% in control) but also 15 times greater in amplitude.

Sensory impairment in addition to motor deficit is considered to be commonly present in children with HCP. Indeed, Krumlinde-Sundholm and Eliasson (2002) described the four most common sensory deficits found in HCP as: tactile perception (sensitivity to pressure), tactile discrimination (spatial discrimination), stereognosis (form/shape recognition) and proprioception (body positon). A recent systematic review (Bleyenheuft and Gordon, 2013) compared the interaction between sensory impairment and precision grip. Thirteen papers were included and tactile perception

was described as impaired in the HCP group in five papers (n=209) spatial discrimination in 11 papers (n=415), stereognosis in 10 studies (n=326), and proprioception in four studies (n=129).

It would be expected that the children participating in the CATCH trial would predominantly present with spasticity although they could have a combination of additional impairments including dystonia, mirror movements and sensory loss.

1.3.2. Activity limitation of the upper limb in HCP

The interplay of the impairments of the bodily structures and functions can lead to limitation in activity or task execution (World Health Organisation, 2013). Considering the array of impairments associated with the affected upper limb in HCP, it is unsurprising that children present with limited activity. Indeed, in a population based study conducted by Uvebrant (1988) in Sweden between 1969 and 1978 it was reported that 50% of children with HCP had either moderately impaired or poor hand function based on their ability to perform eight different hand grips.

Examination of hand function in children with HCP has focused predominantly on the coordination of fingertip forces during manipulation. In a systematic review investigating precision grip control, Bleyenheuft and Gordon (2013) identified 22 studies (n=232). A number of abnormalities in hand function have been described and include; excessive grip force (Eliasson et al., 1995; Gordon and Duff, 1999), disturbed co-ordination of grasp-lift (Eliasson et al., 1991; Forssberg et al., 1999),

abnormal anticipatory control for grip scaling (Gordon and Duff, 1999; Mutsaarts et al., 2006) and prolonged, uncoordinated object release (Eliasson and Gordon, 2000; Gordon et al., 2003). Furthermore, bimanual hand skills demonstrated impaired temporal coordination and a lower correlation of grip forces between hands was found compared to typically developing children (Islam et al., 2011; Smits-Engelsman et al., 2011).

The activity limitations of the upper limb described would be expected to be present in the children with HCP participating in the CATCH trial. The interventions under investigation in the trial specifically aim to offer amelioration of activity limitation in the upper limb.

1.3.3. Developmental disregard

Limited activity in the affected upper limb in HCP results in clumsy movement and possible failure in successful completion of activities. The child may compensate by using only the unaffected upper limb, even for bimanual tasks usually carried out with two hands. This suppression of movement or learned non-use phenomenon was originally described in experimental research conducted on primates (Taub, 1980). Sensation was surgically eradicated from a single forelimb which made movement difficult. Although the primate had sufficient motor innervation they chose not to use the forelimb. A similar finding was demonstrated in adult patients who had sustained a stroke or other type of neurological damage. The patients were typically several months post-stroke and the motor function recovery considered relatively complete.

However, following constraint (a combination of restraint of the unaffected and massed practice of the affected upper limb) the individual was forced to use the affected limb. The intervention unexpectedly led to further recovery in function of the affected limb (Taub et al., 1999; Wolf et al., 2002). Although there has been some controversy over the reasons for effectiveness (Wolf et al., 2002) it has been suggested that following a stroke, patients learn strategies (i.e., learned non-use) that replace the movements that would normally have been assigned to the affected limb (Taub et al., 1999). This results in patients using the less affected limb more frequently, essentially resulting in a reduced need to use the affected limb.

In children this phenomenon has been termed “developmental disregard” (Taub et al., 2004) and it can be demonstrated even when the impairment of the upper limb is relatively mild. Kuhtz-Buschbeck et al. (2000) illustrated an example of this in their study, which examined mirror movements in children with HCP. By simultaneously recording contractions of the active hand (during a unimanual repetitive squeezing task) and fingertip forces of the opposite hand they investigated the frequency and amplitude of mirror movements. This information was correlated with the characteristics of the children’s bimanual functional skills. They found that children who demonstrated mirror movements of the affected upper limb (even low frequency and weak amplitude) usually chose not to use the affected upper limb for bimanual tasks. Instead they used alternative strategies (i.e., disregarding the affected upper limb) such as buttoning clothes with only the unaffected hand. The investigators concluded that the unwanted symmetrical mirroring could hamper the asymmetrical activity required for bimanual skill, therefore was suppressed.

The learned non-use phenomenon of the affected upper limb may not only interfere with the successful completion of functional activity. Overtime it could also lead to secondary musculoskeletal issues (Roberts et al., 1994).

The activity limitations of the upper limb in HCP can lead to movement suppression of that limb resulting in even greater restrictions. Therefore, the investigation in the CATCH trial needed to consider the effects of both the activity limitations and the movement suppression on the affected upper limb function.

1.4. Rehabilitation interventions for the upper limb in HCP

In the UK children with HCP are routinely referred to the NHS for occupational and physiotherapy to provide rehabilitation interventions to address the upper limb dysfunction. The interventions employed have traditionally focused on remediation of the underlying impairments of the body structures and functions (e.g., reducing the effects of spasticity) applying a wide range of intervention strategies. This approach to rehabilitation has been influenced to a degree by a now outmoded classification of disability which focused on the consequence of disease (World Health Organisation, 1980). It was based on the assumption that the impairments of the bodily structures and functions due to disease led to an inability to perform tasks and the combined impairment and disability lead to handicap.

Management of health conditions were influenced by this concept of the consequence of disease and therefore, amelioration focused on impairments of the bodily structures and functions. Boyd et al. (2001) conducted a systematic review of interventions for the upper limb in CP which included; occupational therapy (Case-Smith, 1995; 1996; 2000), neurodevelopmental therapy (Fetters and Kluisick, 1996), peripheral splinting and casting (Blair et al., 1996; Law et al., 1997), conductive education (Reddihough et al., 1998) and the use of adjuncts including Botulinum toxin type-A (Corry et al., 1997; Fehlings et al., 2001). The review concluded that the interventions with the best evidence were occupational therapy and casting, but both demonstrated small treatment effects although, there was growing evidence for injections of botulinum toxin A. However, a key finding from the review was the overwhelming paucity of evidence. Four of the 60 papers included were randomised controlled trials. The reviewers suggested that the development and evaluation of effective upper limb interventions required immediate attention.

In addition to a paucity of supporting evidence, concerns were also raised about the rather narrow and limited view of a chronic disability such as CP depending on interventions which focused solely on bodily impairments (Rosenbaum and Stewart, 2004). In CP this caused a particular issue because the number of possible impairments meant the relative contribution of the individual impairments on the presenting disability, was difficult to ascertain (Sanger et al., 2003).

These concerns were echoed in the new understanding about disability, outlined in a revised International Classification of Functioning, Disability and Health (ICF) from

the World Health Organisation (2001). The ICF provided a classification system where functioning and disability were described in terms of the effects on the individual at multiple levels which were extended to include contexts (personal and environmental factors). However rather than the previous linear causal model, this new updated approach was interactive with all of the components deemed to be important contributors to disability and health rather than just the impairments. Therefore the ICF acknowledged that all aspects of functioning can and probably do affect other areas (Rosenbaum and Stewart, 2004).

A key change influenced by the ICF, was to the conceptual framework that underpinned the treatment of CP. It was no longer perceived as unidirectional (i.e., disability and handicap could only be improved by alleviation of impairment) but bi-directional and interconnected and therefore, could be provided by treatments which accessed the individual at multiple levels and through different factors including context and environment. For example, a child with HCP may be rehabilitated through practice of an activity that is limited (e.g. a task such as grasping a toy). This may not only improve the task but because limited activity is viewed as a result of the interplay of impairments may also provide amelioration of those underlying bodily impairments affecting the task (World Health Organisation, 2013). This was especially important in CP given the array of possible impairments of the body structures and functions and factors such as maturation and growth, which could influence the activity (Sanger et al., 2003). Furthermore, the child may like the toy and therefore be motivated to play which will also impact of the resultant functioning. Figure 1.2 provides a working example of the ICF.

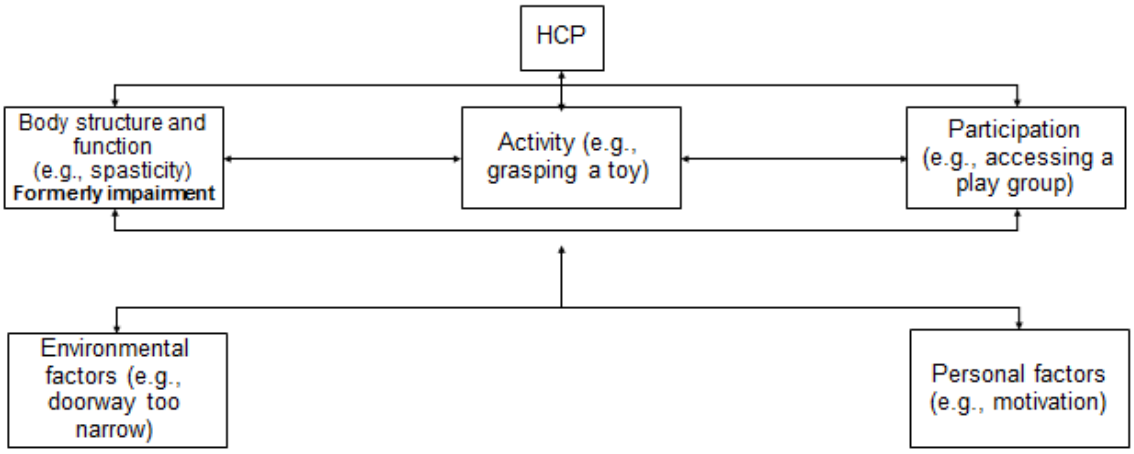


Figure 1.2. The ICF model with HCP as a working example (WHO, 2001 p.9)

Despite the new understanding of disability encouraging a different approach, evidence for upper limb interventions for HCP remained sparse and inconclusive. Sakzewski et al. (2009) conducted a systematic review and meta-analysis on upper limb interventions for children with HCP. Four interventions were identified. Two aimed to effect change of the impairments (i.e., neurodevelopmental therapy (NDT; Brown and Burns, 2001) and intramuscular injections of botulinum toxin (BTX-A) (Reeuwijk et al., 2006). The other two approaches aimed to promote intensive activity and were termed activity-based. Constraint induced movement therapy (CIMT) promoted unimanual practice and hand arm bimanual intensive training (HABIT) involved intensive training of increasingly complex bimanual tasks (Gordon et al.,

2007). The reviewers concluded that none were superior but that activity based interventions such as CIMT warranted further investigation.

More recently Novak et al. (2013) conducted a systematic review on interventions for children with CP. Evidence was classified using a Grade approach (GRADE working group,2004) based on methodological flaws, consistency of results, generalisability of findings and treatment effectiveness. Outcomes on defined populations were given a score reflecting the quality of the evidence (high, moderate, low, or very low). Furthermore, they graded the strength of recommendation for use in clinical practice by weighing up the benefits and harms of using the intervention. This was based on a number of criteria including: estimates of likely benefits and risk; inconvenience; the importance of the outcome; the magnitude of the treatment effect; the precision of the estimate of the treatment effect; the risks associated with the therapy; therapy burden and the costs (Grade working group,. 2004).

The four upper limb interventions (NDT, BTX-A with upper limb training, HABIT and CIMT) identified from the Sakzewski et al. (2009) review were included in the more recent Novak et al. (2013) study. The evidence supporting BTX-A injections was high for both reducing spasticity (Fehlings et al., 2010) and improved function (Boyd et al., 2001; Reeuwijk et al., 2006; Hoare et al., 2010) and strongly recommended for clinical use. However, within this thesis of particular interest were suitable rehabilitation interventions which can be applied within the NHS. A major concern for BTX-A injections is the accessibility for patients to upper limb injections, especially because administration requires anaesthesia. The other impairment based approach,

NDT did not achieve a similar status. Instead, based on the evidence (Butler and Darrah, 2001; Martin et al., 2010) the Novak et al (2013) review concluded that other interventions were more effective. They were unable to rationalise a place for this intervention in current clinical practice. Evidence supporting HABIT was high (Sakzewski et al., 2009, 2011; Gordon et al., 2011) and it was strongly recommended for use in clinical practice (Novak et al., 2013). However, there can be difficulty because it is relatively resource intensive despite a recommendation for group administration. The resource implications can affect applicability within the NHS. The evidence supporting the other activity based intervention, CIMT was considered moderate (Hoare et al., 2007; Huang et al., 2009) although it was strongly recommended for use in clinical practice (Novak et al., 2013).

Four upper limb interventions for children with HCP were identified. However, supporting evidence for one was limited (neurodevelopmental therapy) and it was considered that two interventions (BTX-A with upper limb training) and HABIT) could be difficult to administer within the NHS. Therefore, of the four interventions CIMT, which has supporting evidence and considered potentially suitable for application within the NHS was investigated to address the upper limb in HCP in the CATCH trial.

1.5. Constraint induced movement therapy (CIMT)

The fundamental principle of CIMT is the provision of mass practice of the affected upper limb for individuals with a unilateral impairment such as HCP to improve

functional activity, by overcoming learned non-use or movement suppression (Taub et al., 1993; 1999). CIMT has been classified within the ICF model as targeting an individual's activity (task execution) (Novak et al., 2013; Sakzewski et al., 2009). However, the intended outcomes of interventions can be refined further because the ICF provided a means of classifying the extent at which an individual's activity is affected and therefore, how it may be ameliorated by using qualifiers (i.e., performance and capacity). Performance is observable and describes what a person does in their actual environment, therefore, reflects actual or usual functioning in a real life setting. Capacity describes the individual's best practice in a standardised evaluation setting and related only to limitations due to the health condition (World Health Organisation, 2013). An expert consensus on CIMT stated the goal of CIMT was to gain improvement of the upper limb in the usual or current environment during everyday activity (i.e., performance) predominantly in two-handed activities.

Bimanual skills are considered the main focus of the CIMT intervention because children with HCP rarely use their affected upper limb for unimanual tasks. Instead it is typically used when it is required, during bimanual tasks (Greaves, 2010). It is these two-handed tasks that typically may be compromised by amongst other factors, suppression of movement (learned-non-use) which CIMT has been developed to specifically target (Taub et al., 1999). However, during administration of the CIMT unimanual skills are practiced with the affected upper limb because restraint of the unaffected upper limb is in situ. Consequently, CIMT could also impact on the unimanual capacity of the affected upper limb (Eliasson et al., 2013). Therefore, in the CATCH the primary target was improvement in bimanual performance of the

affected upper limb however, unimanual capacity of the limb is also predicted to improve.

The original model of CIMT was developed by Taub and colleagues (1993; 1999) and consisted of two distinct parts (i.e., movement restriction and training). Both of which aimed to induce, intensive use of the affected upper limb. The training procedure was an approach called “shaping” described as operant movement conditioning. Discrete tasks were subdivided and practiced in measurable chunks and made increasingly difficult. In addition, patients were encouraged with frequent verbal reinforcement (Taub, 2004). The movement restriction was offered by a hand restraint and arm sling of the unaffected upper limb to promote increased use of the affected upper limb. This original package was developed for adults with stroke and involved restraint for 90% of waking hours and intensive training of the involved upper limb for six hours per day for a period of two weeks It demonstrated a treatment effect for adult stroke patients at 12 months in a large (n=222), prospective, randomised, multicentre clinical trial (Wolf et al., 2006). Timed functional performance improved statistically significantly in the CIMT group compared to the control with a group difference of 34% (95% CI: 12%, 51%, p<.001) and in the amount of use (on a 0-5 scale) with a group difference of 0.48 (95% CI: 0.13, 0.84, p<.001).

Over time there were adaptation made to the original CIMT package in terms of the type of training, the number of hours of daily exercise and the method of restraint. Sirtori et al. (2009) conducted a Cochrane systematic review on efficacy for the upper limb in the adult stroke population which included 19 studies (n = 619). Although,

positive short-term effects were demonstrated there were a number of methodological flaws of the included studies. Many were small and underpowered and only about half described the randomisation process. It was considered likely that patients were excluded post-randomisation or blinding not maintained. Furthermore, data reporting was poor with some studies only reporting significant differences between groups. Only five studies reported long term effects. Given the bias in the individual studies, the reviewers recommended further research.

There are conceptual differences in the use of CIMT for adults who have had a stroke (an acquired lesion on a mature brain) and children (an insult on a developing brain). However, the essential components of CIMT aimed to reverse the behavioural motor suppression whether it was acquired (i.e. learned non-use) or (developmental disregard) and the result of a congenital condition (Hoare et al., 2007). Therefore, CIMT has been administered as an upper limb intervention for children with HCP. A critical review of CIMT in children with HCP (Charles and Gordon, 2005) included fifteen studies (n = 160) which the authors described as showing promising results in improving upper limb function. However, most were case studies (n = 8) and only four (n = 93) compared outcomes with a control group (Willis et al., 2002; Taub et al., 2004; Eliasson et al., 2005; Charles et al., 2005). A meta-analysis or synthesis was not conducted of the controlled trials due to the variability of the intervention and outcome measures although, all reported significant improvements in upper limb function. It was recommended that larger scale RCTs were needed to inform efficacy and possible implementation into clinical practice.

A Cochrane systematic review was conducted to evaluate the effectiveness of CIMT in the upper limb in children with HCP (Hoare et al., 2007). It included three studies (n=90) and of those one (Eliasson et al., 2005) provided support for the efficacy in the HCP population. A meta-analysis was not conducted, because of the inconsistency of the outcome measures in the included trials. One study, a case controlled trial (CCT) (n=41) showed a statistically significant treatment effect on upper limb activity performance measured with the Assisting Hand Assessment; (AHA; Krumlinde-Sundholm et al., 2007; Krumlinde-Sundholme and Eliasson, 2003). The mean change scores at two-months were (SMD 1.12, 95%; CI: 0.46 to 1.78) and six months (SMD 0.74, 95%; CI: 0.10 to 1.37). Given the non-randomised nature of group allocation it was unclear however, if the groups were the same at baseline (Sedgwick, 2013). Deluca et al. (2006) conducted an RCT (n=18) which demonstrated a positive trend only on one subscale (movement dissociation) of the Quality of Upper Extremity Skills Test (QUEST; Dematteo et al., 1992). This was at three weeks post-treatment (SMD 0.91; 95% CI:-0.08 to 1.89). The third study (Sung et al., 2005) an RCT (n=31) showed a statistically significant improvement (SMD 1.25; 95% CI: 0.46 to 2.03) on the self-care component of the Functional Independence Measure for Children (Wee-FIM; Msall et al.,1994) at six-weeks. However, Hoare and colleagues (2007) recommended that this result be viewed with caution, because of the lack of methodological rigour, ambiguous methodology and inadequate reporting. All other outcome measures included in the Cochrane systematic review (2007) showed no significant treatment effects.

The reviewers concluded that evidence for the use of CIMT was promising but there was a need for further evidence to support its use in practice. It was therefore timely to conduct the clinical trial to investigate the use of CIMT for functional improvement in the upper limb in HCP.

1.6. Overview of the thesis

This chapter has summarised the relevant background literature in terms of CP and its subgroup HCP. It has provided an overview of the deficits and activity limitations of the upper limb in HCP and current rehabilitation interventions. An outline is given of the reason for conducting research to evaluate the efficacy of CIMT for the upper limb in HCP. **Chapter 2** will continue with a discussion of the main theories of motor learning to provide a theoretical framework to underpin the development of an intervention and provide a structure to discuss the study findings. **Chapter 3-7** describe a randomised controlled trial to compare two methods of constraint induced movement therapy to improve functional ability in the affected upper limb in pre-school children with hemiplegic cerebral palsy (CATCH trial). This trial protocol aims to evaluate the feasibility of a novel CIMT model and its effectiveness in terms of improving upper limb function within an NHS environment (**Chapter 3**). The results from the CATCH pilot trial are reported in **Chapter 4** and an overview of the parent and nursery worker reported outcomes on fidelity are provided in **Chapter 5**. A thematic qualitative analysis examining the consequence from the parent, guardian, and nursery worker perspective of intervention implementation is reported in **Chapter 6**. In **Chapter 7,** the development and psychometric validation of a parent-reported

tool to measure assisting hand function of an affected upper limb in pre-school children with HCP will be discussed (Birmingham Bimanual Questionnaire). Given the findings from the CATCH trial, an updated systematic review and meta-analysis were conducted and outlined **(Chapter 8).** In the final part of the thesis **(Chapter 9)** the main findings and implications of the thesis will be discussed and suggestions for future research made.

Chapter 2: Motor learning theories

2.1. Introduction

The ability to learn motor skills is an essential part of normal child development and can be observed from how a baby progresses from total dependence to be able to carry out tasks of daily life and function in society. However, a child with cerebral palsy (CP) will be limited in their ability to acquire motor skills, because of their array of impairments. Therefore, a fundamental purpose of therapeutic interventions for children with CP is to provide the possibility of (re)-learning motor skills to enhance independence and participation. This chapter will introduce the main theories of motor learning and discuss how they may provide a theoretical underpinning of the interventions examined in the investigation reported in this thesis.

Motor learning can be described as relatively permanent change in the capacity for skilled movement, associated with practice or experience (Schmidt and Lee, 2011). Theories that underpin motor learning may be based on information processing where movement is not merely a response to a stimulus but the result of processed information. A memory representation of the skill is required for this to occur. Examples of such theories are Adams' closed-loop theory (Adams, 1971) and Schmidt's schema theory (Schmidt, 1975). On the other end of the spectrum is the paradigm called the dynamical and ecological approach to motor learning (Gibson, 1988;Kelso, 1995). This alternative paradigm rejects the notion of a memory

representation but instead focuses on the changing relationship between the learner, the task and the environment.

2.2. Adams' closed-loop theory of motor learning

Schmidt and Lee (2011) use the regulation of the temperature in a room with a thermostat as a classic example of a closed-loop system. The preferred room temperature (i.e., reference temperature) is set through a thermostat. When the temperature in the room falls below the reference temperature, the thermostat turns the radiator on to heat the room. The thermostat constantly measures the room temperature and feeds the information back to the system (i.e., central heating system). Once the reference temperature in the room has been reached, the thermostat turns the heating system off. The essential part of this closed-loop system is that information about the room temperature is monitored and fed back (i.e., through the thermostat) to maintain the reference temperature via the radiators. Adams was the first to develop a motor learning theory and based it on such a closed-loop system (Adams, 1971). The theory focuses on learning simple, self-paced, linear movement to a correct endpoint (i.e. a target or object) through feedback.

The basis of Adams' closed-loop theory is that two distinct states of memory can be defined, which are independent but not mutually exclusive. The recall trace is a simple set of muscle commands stored in the memory (i.e. a motor programme) and responsible for the selection and initiation of a motor response. This could include

pointing to a toy or grasping an object. Once the motor response is initiated, the perceptual trace acts as an internal reference, responsible for guiding the movement towards the correct endpoint. The assumption in the theory is that there is a perceptual trace stored in the memory which has been generated from previous experience of similar movements. In the example of the central heating system given above the reference of the movement is equivalent to the preferred room temperature set within the thermostat. The sensory information generated from the movement is compared against the reference (i.e., the expected outcome of the movement). If the expected movement has not been achieved, then the movement is corrected and the cycle continues until it has. According to this theory, a movement is learned through the strength of the recall and perceptual trace. For example, when a child learns to point to a toy, there will be an error between the intended and actual movement towards the toy. The system (i.e., the child) will become aware of the error and respond with a new motor response. These steps will continue until the limb reaches the toy (i.e., correct end point has been achieved; Adams, 1971).

A central aspect of this theory is confirmation of our outcome of the movement (i.e. knowledge of results (KR). As the learner becomes more practiced in this particular movement, the strength of the recall trace becomes stronger (i.e. the muscle commands becomes more finely tuned in terms of time and force). In turn, the perceptual trace becomes more clearly defined, which further enhances the strength of the recall trace (Schmidt and Lee, 2005). A schematic representation of how movement is learned according to Adams' closed-loop theory (based on the

diagrammatic elements of a closed loop system (Schmidt and Lee, 2011, p.136) is presented in Figure 2.1

2.2.1. Therapeutic practice underpinned by Adams' closed-loop theory

A therapeutic intervention that is underpinned by Adams' closed-loop approach to motor learning would practice simple, self-paced, slow, linear movements, repeatedly to the same endpoint. For instance, the child is asked to repeatedly reach in a unidirectional manner (i.e., the same distance and direction) towards a target. The therapy is offered within a controlled environment (e.g., outpatient clinic or hospital environment) where aspects such as the position of the target can be controlled. The sensory feedback of the reaching movement is expected to guide subsequent movements until the correct endpoint is reached. Once that endpoint is successfully attained, the movement can be considered as learned. Therefore, motor learning is dependent upon repeated practice of a movement to exactly the same endpoint. The provision of KR (i.e., confirmation of the movement outcome) through a therapist or from feedback technology is central in this theory and will enhance the learning of the movement (Adams, 1971).

2.2.2. Review of Adams' theory

This theory of motor learning only deals with movement that is of a sufficiently slow frequency to be able to respond to feedback and therefore does not include learning

of fast movement. In addition, it only accounts for how existing movements become more efficient and accurate, not how novel movements are learned. This is because a motor response can only be initiated if a recall and perceptual trace from a previous movement is present. Furthermore, the theory assumes that for every possible movement, there is a corresponding recall and perceptual trace stored. The endless amount of information that needs to be stored, pose a problem for the CNS (i.e., storage problem). The novel and storage problems in Adams' theory was argued to be major shortcomings by Schmidt (1975) who integrated some of the basics from this theory into an alternative model which introduced the concept of generalised motor programme.

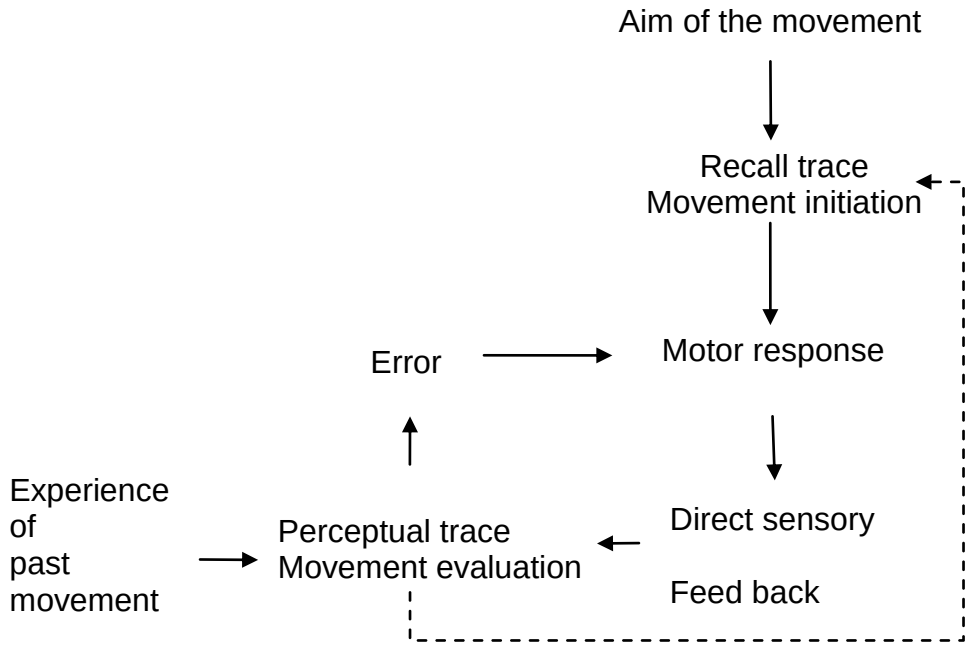


Figure 2.1. Motor learning according to Adams' closed-loop theory
(based on Elements of a closed-loop system (Schmidt and Lee, 2011, p.136)

2.3. Schmidt's schema theory

2.3.1. Generalised motor programme (GMP)

The basis of Schmidt's theory (1975) is the presence of generalised motor programmes (GMPs), which are assumed to control a type of movement rather than an individual movement. Examples are drawing, writing or throwing which have certain invariant features, which may include the sequence of sub-movements relative timing or force. However, it was assumed the GMPs could be adapted to specific situations if required. In Figure 2.2 adapted from (Schmidt and Lee, 2011, p.209) the example shown is writing which has invariant features, implied by the similarities between the letter formations. This seems to suggest an underlying GMP. However, the GMP needs to be adapted based on the specific situation (i.e., writing with the dominant hand, the non-dominant hand and with a palmar grasp; see Figure 2.2). Schmidt, refers to this as the adaptation of the GMP's parameters and in this example, the parameter refers to the use of different muscle groups or effectors (Shea and Wulf, 2005). Therefore, the existing GMP controlling the movement can be adapted for different effectors or different tools such as writing implements.

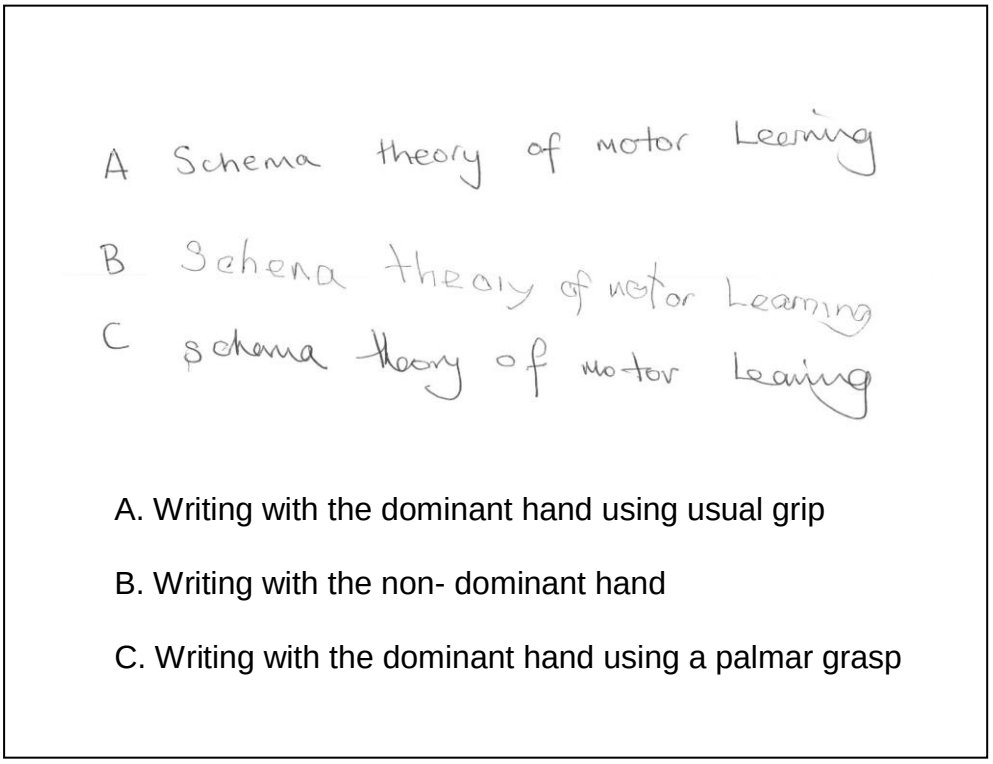


Figure 2.2. Invariant features of the GMP

(adapted from (Schmidt and Lee, 2011, p.209)

2.3.2. The schema

Schmidt incorporated aspects of Adams' closed-loop model (1971) into his theory of motor learning, (i.e., two separate memory states). Unlike Adams who focused on slow movements where sensory feedback can be processed to guide subsequent movement, Schmidt (1975) wanted to explain the coordination of high velocity movements. Therefore, sensory feedback could not act quickly enough to guide the movement, but instead was fed back to update the schema and retained as stored information.

The stored information from previous movement experiences can be categorised as: 1) the initial movement conditions; 2) the movement parameters used; 3) the sensory consequences of the movement (i.e., intrinsic feedback); and 4) the movement outcome (i.e., KR). Through practice of the movement type, the learner forms stronger relationships between the four classes of stored information, which Schmidt refers to as recall and recognition schemas (Schmidt, 1975). Before a movement is initiated a recall schema is selected, based on the aims and initial conditions of the current movement and the stored information from previous movements. The recall schema is then coupled with a GMP and makes the relevant adaptations for the specific situation. For example, if the intended task is catching a ball, a GMP for catching is coupled with a recall schema from previous experience of catching a ball. A copy of the recall schema is made available to the recognition schema, which acts as a reference that the movement has been performed correctly (i.e., the ball has been caught). Any mismatch between the schemas produces an error, which is fed back to update the recall schema. Therefore, as a movement is practiced and learned the recall schema is updated through error detection and becomes stronger in terms of movement, accuracy and fluency. In this theory, motor learning refers to the parameters or changes in the GMP not the GMP itself. The GMP and recall schema, which control the parameters are proposed as separate memory representations (Schmidt, 1975). A schematic representation of how movement is learned according to this theory based on a diagrammatic representation (Schmidt, 1975, p.238) is outlined in Figure 2.3.

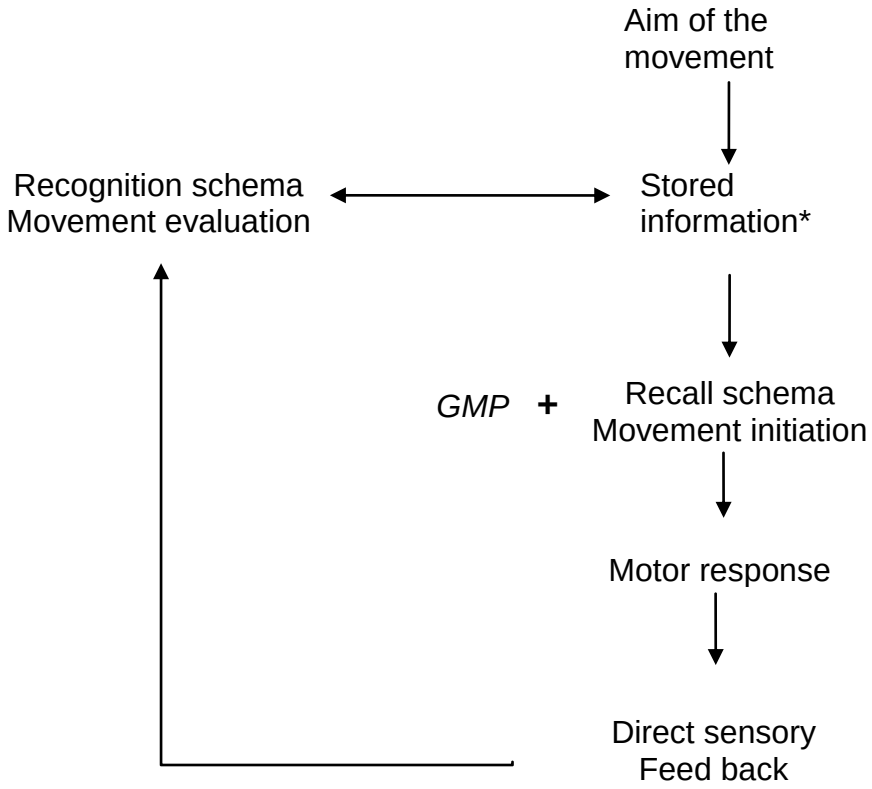


Figure 2.3. A schematic representation of motor learning according to Schmidt's schema theory.

Based on (Schmidt, 1975, p.238)

(*)stored information about past movement which includes (1) the initial movement conditions; (2) the movement parameters used; (3) the sensory consequences of the movement or intrinsic feedback; and (4) movement outcome (KR).

2.3.3. Therapeutic practice underpinned by Schmidt's schema theory

Feedback on movement outcome (i.e. knowledge of results; KR) is considered to be important in updating the schema and has been extensively researched. For example, Sullivan et al. (2008) compared the effect of 100% KR to reduced KR (62% faded) in both young adults and typically developing (TD) children during practice of 200 (4 sessions x 50 trials), carrying out a simple, discreet movement (i.e., moving a

lightweight lever that was restricted to movement in an horizontal plane). At the beginning of each trial a target trajectory (i.e., a position-time trace) was shown on a computer screen. Following this, the participant was asked to replicate the trajectory with the lever. Post completion, augmented feedback was displayed on the computer screen for every trial (100% feedback) or gradually reduced over the sessions to 62% of the trials. The feedback consisted of a numeric error score and a graphic representation of the participants response superimposed on the target movement pattern. Skill acquisition was measured by comparing the error difference between the target trajectory and the participant's response. As might be expected, error reduced with practise. It was interesting to note that performance accuracy was similar in adults regardless of whether feedback was reduced but in children, performance was improved with 100% feedback ≥ 75% relative feedback frequency was noted as a critical point). Similarly, retention measured using error difference on the following day was similar for adults regardless of feedback but significantly less accurate for children who had received less feedback. The authors hypothesised that children may require longer periods of practice with feedback to form a more stable schema or CNS representation of a motor skill to optimise motor learning.

2.3.4. Review of Schmidt's Schema Theory

The notion of a stored set of muscle commands ready for action (i.e. the motor programme) has been supported in a number of ways. The primary evidence is that numerous movements can be carried out in far less time than it takes for the feedback loop to operate. For example, a boxing punch has a movement time (MT)

of approximately 40 milliseconds which offers little possibility for feedback to influence the outcome (Schmidt and Lee, 2011). Furthermore, in an experiment carried out by Wadman et al. (1979), participants were asked to move their arm to targets using rapid elbow extension. The activity of the agonists and antagonists were measured using EMG. In some trials the experimenters would unpredictably block the limb from moving from the starting position. The initial activity of the agonists and antagonists were the same whether the limb had been blocked or not. The authors argued that these observations support the notion that movement is pre-defined with a generalised motor programme. Schmidt, (2003) suggests that this is amongst the strongest evidence of the existence of motor programmes.

The introduction of the GMP into the theory provided Schmidt with a solution to Adams' storage problem because of the reduced amount of memory representations required (Shea and Wulf, 2005). However, Schema theory predominantly focuses on learning an updated or refined version of a pre-existing movement which is represented in the GMP. The novel problem (i.e., learning totally new movements), which was a weakness of Adams' closed-loop theory, was not solved. Indeed, in his reflection on the Schema theory, Schmidt (2003), himself acknowledged that the lack of account of how novel movements are learnt is a fundamental flaw. He attempted to provide a solution to the storage problem, which was a limitation in Adams' closed-loop theory, with the GMP. However, the question still remained on how such detailed information could be stored on the large number of inherent factors within joints and muscles that have to be controlled in different contexts for every motor task. An alternative proposal came from Bernstein (1967) who proposed that only a

limited amount of movements were possible with an infinite amount of inherent factors. This became known as mastering the degrees of freedom and will be discussed in more detail in the next section.

2.4. The dynamical and ecological approach to motor learning

The dynamical and ecological approaches to motor learning are separate theories but they share many common features and assumptions. Therefore, they are usually described as one approach in the literature, although their initial implementations could not be further apart (Rose and Christina, 2006). The concepts associated with the dynamical approach can be traced back to the synergistic theory (Haken, 1977), which relates to spontaneous pattern formation in nature (i.e., cloud formation and movement between molecules). However, the ecological approach of direct perception (Gibson, 1979) is associated with the interaction between a person and their environment. The dynamical and ecological approach to motor learning has been advanced by a number of prominent researchers including; Fowler and Turvey (1978), Newell (1986), Newell (1991) and Kelso (1995). A broad description in the following paragraphs will form an introduction to the main features and assumptions of the dynamical and ecological approach.

2.4.1. Mastering the degrees of freedom

It is assumed that the muscles and joints in our body offer an endless amount of movement options. The cornerstone of the dynamical and ecological theory is that a movement is learned and expertly performed by the constraint of individual muscles and/or joints, to form a single unit of control (Bernstein, 1967). The formation of single units reduces the number of movement options available. However, the advantage is that it increases the level of control over the movement (Fowler and Turvey, 1978). Expert movement occurs when the redundant degrees of freedom (i.e., individual muscles and/or joints) are mastered into a single unit of control. For example, when a baby first learns to grasp, they initially use a palmar grasp which involves using all the fingers and the thumb together. However, as their hand skills mature they will develop a pincer grip (activation of the index finger and thumb only) which enables greater dexterity and fine manipulation. This is achieved by mastering the redundant degrees of freedom (i.e., the remaining joints and muscles of the hand are coordinated into a single unit). This can be observed when comparing the palmar grasp of a 12 month old with a pincer grip of a five year old child (Exner, 2005).

Newell (1986) advanced the theory to include the formation of functional, coordinated motor patterns. He recognised the complementary relationship with the task and, the influence of the environment. A schematic overview of the constraints (i.e., organism, task and environment) which influence motor pattern formation for coordination and control are shown in Figure 2.4. Indeed, in an experimental example, Newell et al. (1993) demonstrated that babies as young as 5 months changed the configuration of grip according to the object-hand size ratio (i.e., the grasp changed according to the

size of the cup they were given). They systematically increased the number of digits as the size of the object increased. Newell et al. (1993), argued that the babies coordinated their motor action with the information about the cups, which they received perceptually, from the environment (not from a pre-defined motor pattern). Furthermore, they found that both groups (adults and babies) used only a very small set of possible grip configurations. Five different grips accounted for 91% of infants and 95% of adult grips. They suggested that object size was a particularly strong constraint on grip configuration.

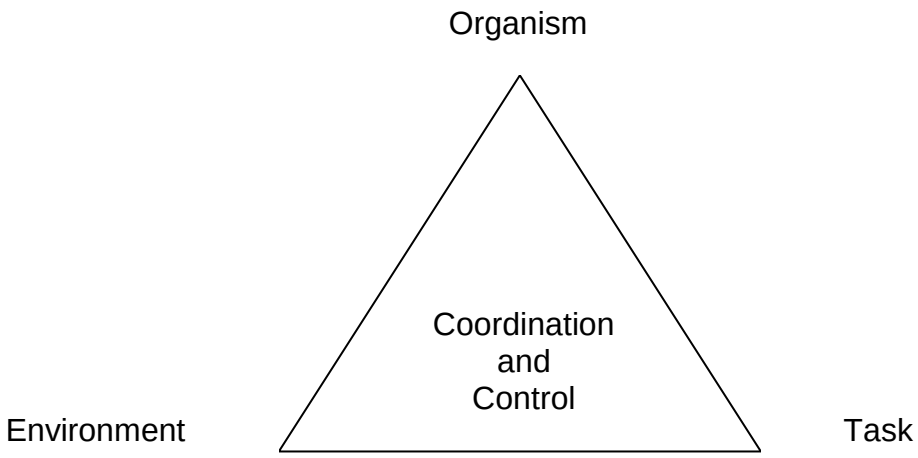


Figure 2.4. A schematic overview of the categories of constraint for optimal pattern formation for coordination and control.

(Newell, 1986, p. 348) Printed with permission

Mastering the degrees of freedom into a single coordinated unit provides a platform on how an infinite amount of inherent factors within joints and muscles can be controlled, to enable complex motor tasks to be performed. However, the interaction between the constraints can be considered as self-organising and the spontaneous adaptations that are required are not accounted for in the theory. Therefore, expansions of the degrees of freedom approach were required. This led to the assimilation with the dynamic pattern theory which will be discussed in the next section.

2.4.2. Dynamic pattern theory

A more detailed model, to explain self-organisation in relation to spontaneous motor pattern formation, and abrupt transitions from one pattern to another was provided by Kelso (1995) in dynamic pattern theory. To discuss the theory, an example is given from observation made by Kelso (1995, p.47) during his classical experiment. In most people the index fingers can be oscillated in only two stable coordinative patterns: 1) in-phase (i.e., both fingers move up and down together) and 2) anti-phase (i.e., alternate fingers move up and down). Anti-phase movement can be performed at low movement frequency. When the speed of the movement increases, the coordinative pattern becomes more unstable and eventually spontaneously switches into the in-phase pattern. The in-phase coordinative pattern is maintained (stable) when the movement frequency is further increased. When this experiment is repeated with the in-phase pattern, a transit between coordination patterns does not occur. In dynamic pattern theory, the relative movement between the fingers or the coordinative structure of the emerging motor pattern is referred to as the order parameter. The theory predicts that the movement can abruptly transit from one order parameter (coordinated patterns) to another, in response to a change in the control parameter (i.e. movement frequency; Kelso, 1995).

The spontaneous transit (i.e., self-organisation) between order parameters or coordinated patterns caused by changes in the control parameter was mathematically modelled by Haken, Kelso and Bunz (HKB-model; Haken et al., 1985). Graphically, this can be depicted by a potential landscape as shown in Figure

2.5. The potential landscape of the HKB model has local troughs and peaks, which represent stable and unstable coordination patterns, respectively. In the example of the bimanual finger oscillation, the anti-phase coordination pattern is a trough (i.e. stable state) at low movement frequencies. When the control parameter (i.e. movement frequency) is increased, the trough becomes shallower and eventually becomes a peak (i.e. unstable state). The movement, represented by the black sphere, in Figure 2.5 (Kelso, 1995) is attracted towards the stable state (deep trough) and a transit from anti-phase to in-phase coordination pattern occurs. The potential landscape is maintained as the movement frequency increases, which predicts that the in-phase coordination pattern is a stable state at both low and high movement frequencies. This mathematical model provides a platform to describe how variations in the control parameter can affect the movement in terms of transit between coordination pattern states. It can be used to describe how, through the manipulation of the individual, task and/or environment a movement can be (re-)attracted towards a stable state.

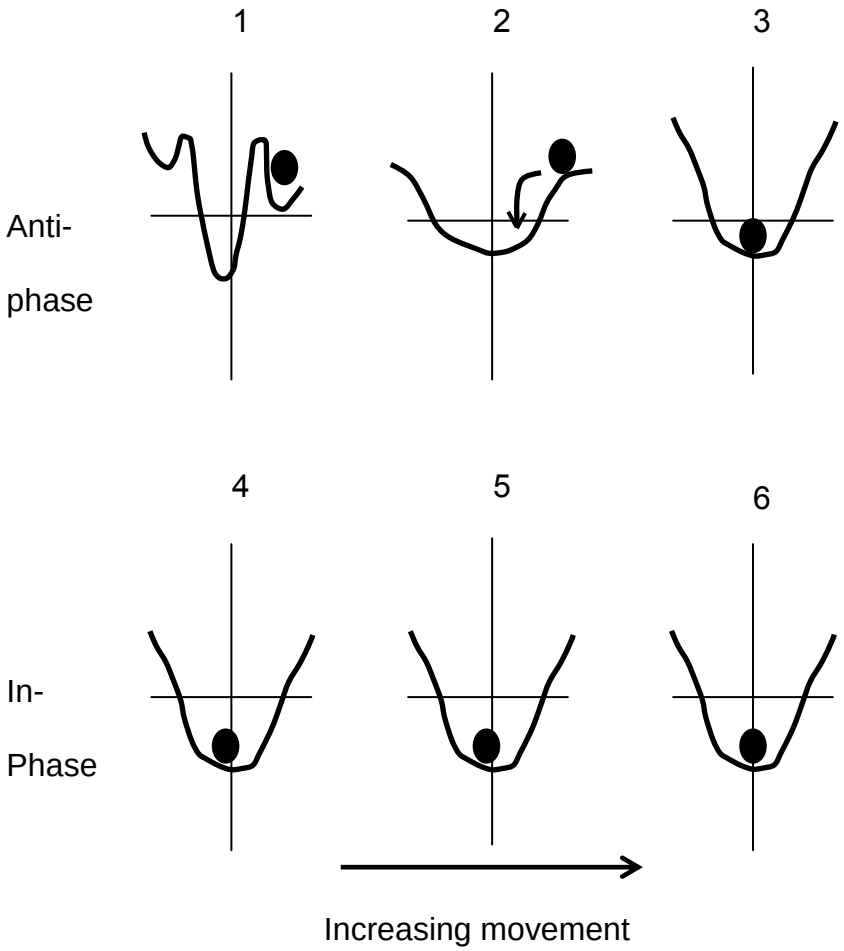


Figure 2.5. The HKB model:

The potential landscape or phase stability of bimanual coordination during rhythmical oscillation, with increasing movement frequency. The black sphere represents movement. During anti-phase coordination shown in the top panel, the increased movement frequency leads to a change from a stable trough (1), to a more unstable peak (2) and then to a stable trough (3).This represents a transit from anti-phase to in-phase coordination. The lower panel (4-6) represents in-phase coordination and

shows a stable trough with increasing movement frequency which represents stability at both low and high movement frequency (adapted from Kelso, 1995, p.55).

2.4.3. The ecological approach to action and perception

Gibson (1979) emphasised the importance of the mutuality between the learner and the environment in his ecological approach to the development of action and perception. The learner is thought to be able to perceive relevant information from the environment, which directly relates to the coordination of movement. In turn, the movement has a direct effect on the environment. This circular relationship is referred to as the action-perception coupling. In order to describe this circular relationship between the action performed by the person and the relevant information available from the environment, Gibson (1979) coined the term affordances For example, when considering a child grasping an object the affordance is what can be done with the object based on its inherent properties (e.g., its size, shape and texture). It may be a large, round object with a textured surface which enables it to be grasped whereas, a small, oblong, slippery object cannot. Therefore, affordances will influence the learner's actions. The place where this information can be found is the interface between the learner and the environment called the perceptual-motor workspace (Newell, 1991).

2.4.4. Therapeutic practice underpinned by the dynamical and ecological approach

In a cluster RCT conducted by Law et al. (2011), 128 children with CP with a mean (SD) age of 3 years 6 months (1 year 5 months) received either a child focused or a context focused intervention. In the child focused approach, impairments were identified (e.g. spasticity). Impairment-based therapy (e.g., neurodevelopmental therapy (NDT)) was provided in addition to practice of specific movements and tasks. The context therapy approach emphasised changing the task and/or the environment rather than the child's impairments. The tasks chosen depended on what the child was interested in or trying to perform. Constraints within the task, environment and or the child hindering success were identified. Treatment involved changing the identified constraints. The primary outcome was performance of functional tasks (mobility and self-care) measured by the Paediatric evaluation of disability inventory (PEDI; Haley et al., 1992. There was no significant difference between the outcomes of either group although both significantly changed from baseline to the six month follow-up. The findings from this RCT would be predicted from a dynamical and ecological approach to motor learning, because the task and environment are considered to be as important as the child.

2.4.5. Review of the dynamical and ecological approach to motor learning

From this approach movement is presumed to be learned by finding the most appropriate action to couple with the perception of the affordance (Savelsbergh et al.,

2003). This is in contrast to learning movement by a reproduction of a static representation of movement, (i.e. Schmidt's schema theory (1975) and Adams' closed-loop theory (1971). Moreover, the information to evoke an action is assumed to be in the environment, rather than stored in the CNS of the individual (Savelsbergh et al., 2003). The dynamical and ecological approach, therefore, provides a solution to the novel and to the storage problems faced by information processing.

The direct relationship between action and perception seems to offer many benefits to describe motor learning. However, a substantial limitation to the approach is the lack of account for any cognitive processing. Indeed, it would be difficult to consider learning motor tasks and improving performance without cognition. Motor imagery is the internal reproduction of a movement without any actual movement being produced and requires cognitive processing. To investigate the mechanism underlying motor imagery Mulder et al. (2004) investigated its effect on a completely novel task (i.e., abduction of the big toe). Participants were divided into those who could not abduct their big toe (absolute zero group) and those that could (partial group). Each group were sub-divided to a control, or to undertake mental practice (MP) or physical practice (PP) group. Changes in big toe abduction were measured with EMG. Both control groups remained the same and both the PP groups improved significantly ($p<0.001$). However, although the MP partial group improved significantly ($p<0.001$) the MP absolute zero group did not ($p=.70$). Motor learning from the perspective of information processing would predict this because the absolute zero group would not have a memory representation of the big toe abduction and therefore, could not improve on the task with MP.

2.5. Chapter summary

The inefficient movements and motor failure of the affected upper limb in hemiplegic cerebral palsy (HCP) may lead to suppression of future attempts. Furthermore, the child may learn to compensate for most tasks by using only the unaffected upper limb. Constraint induced movement therapy (CIMT) aims to promote mass practice of the affected upper limb and the theoretical framework underpinning the intervention could be explained from the perspective of both motor learning paradigms.

From the information processing approach (Adams' closed-loop and Schmidt's schema theories) the child may have the required (generalised motor programmes) GMPs stored in memory from previous experiences. However, the effector of the GMP (i.e., part of the body that is executing the predetermined motor pattern) is predominantly the unaffected upper limb. Therefore, there is limited opportunity for a memory representation which involves the affected upper limb to be developed. CIMT changes how a movement is executed, by changing the effector of the GMP towards the affected upper limb. It is assumed that as movement with the affected upper limb is practiced, more information is assimilated to develop and refine the memory representation in the schemas. In turn, this increases the potential for motor learning with the affected upper limb.

According to the dynamical and ecological approach to motor learning the lack of use of the affected upper limb means that the child does not use it within the perceptual-motor workspace. The child therefore does not have the opportunity to

spontaneously develop coordinated movement patterns based on the interplay between their affected upper limb, the task and the environment. There is limited opportunity to explore the environment and find the opportunities available or affordances, for the task at hand. CIMT acts as a control parameter, which has the potential to shift exploration of the environment towards the affected upper limb and influence the development of coordinated movement patterns or order parameters, of this limb. A movement such as grasping an object may spontaneously transfer away from a more stable state (i.e., grasping with the unaffected hand) towards a (previously) less stable state (grasping with the more impaired hand). Therefore, it is assumed that CIMT provides opportunity to develop coordinated motor patterns, which include the affected upper limb. Although the underlying assumptions from these approaches to motor learning are fundamentally different, they both advocate mass practice to influence motor learning and improve movement of the affected upper limb in children with HCP.

Chapter 3: Methodology for a randomised controlled trial

3.1. Introduction

This chapter will present the trial undertaken to compare two methods of constraint induced movement therapy (CIMT) to improve functional ability in the affected upper limb, in pre-school children with hemiplegic cerebral palsy (CATCH). The development, piloting and evaluation of the intervention under investigation, was guided by the framework provided by the Medical Research Council (2006) and will be described in the first part of the chapter. The rationale for the trial design will be outlined followed by the aims and objectives. The trial methodology will be described which followed the guidelines for reporting randomised controlled trials outlined in the CONSORT statement (Schulz et al., 2010) in conjunction with the CONSORT (2010), explanation and elaboration document extended to non-pharmacological treatments (Boutron et al., 2008). Furthermore, the Template for Intervention Description and Replication (TIDieR; Hoffman et al., 2014) guided the intervention descriptions (see Appendix 2 for the TIDieR checklist).

3.2. Aims and objectives of the trial

The aims of the CATCH trial were to determine the efficacy of a novel approach to CIMT with a prolonged restraint methodology for pre-school children with HCP. The objective was to establish whether CIMT with prolonged restraint was more effective

than a usual NHS CIMT. In addition, the feasibility of conducting a RCT within an NHS community paediatric environment was evaluated in order to assess and revise the design for a definitive trial. The objective was to establish whether participants could be recruited and retained on the CATCH trial and to determine whether the trial procedures including randomisation and blinding were acceptable and the intervention was safe. It should inform the design of a definitive trial and provide sufficient justification to plan a larger multi-centre trial to look at longer term outcomes and an economic evaluation.

3.3. Development, piloting and evaluation of a complex intervention

Many health care interventions such as CIMT contain several interacting components and as such are described as complex (Medical Research Council, 2006). To guide researchers on their development and evaluation the Medical Research Council (2006) have developed guidelines which include four stages; development, feasibility and piloting, evaluation and implementation (see Figure 3.1). These guidelines have been closely adhered to in order to guide the development, feasibility, piloting and evaluation conducted within the CATCH trial.

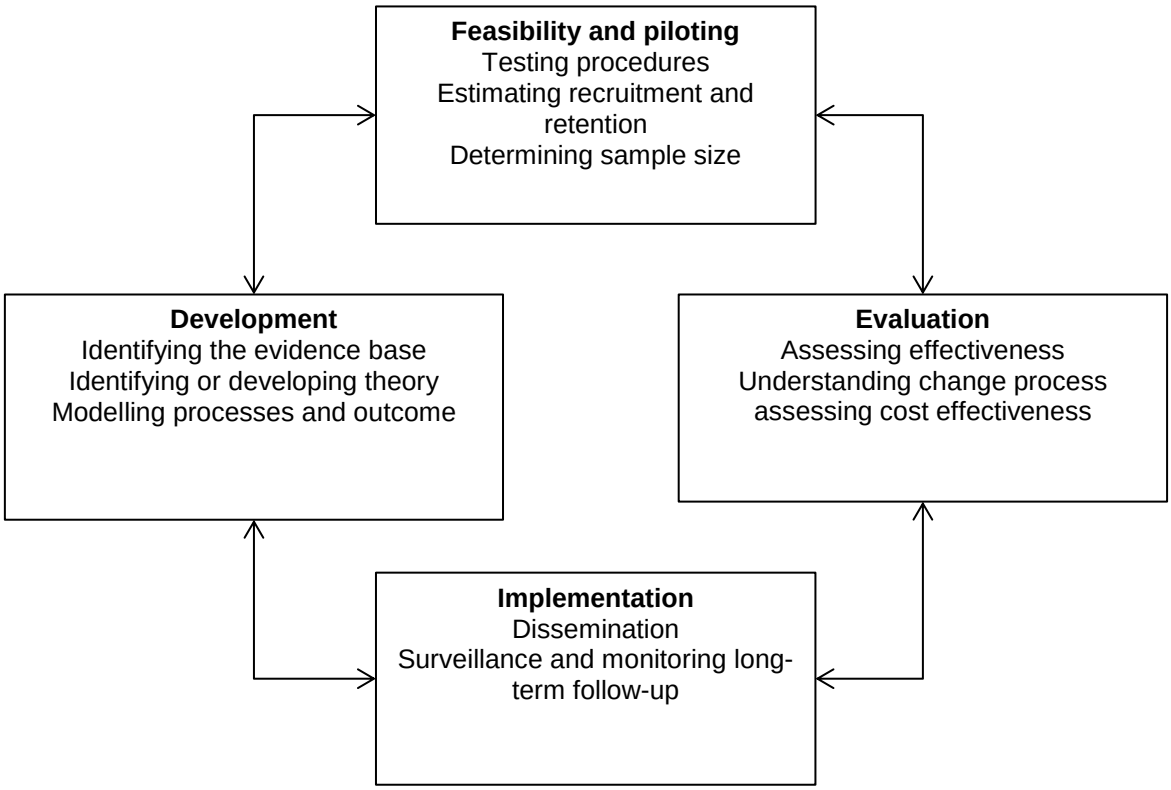


Figure 3.1. Key elements of the development and evaluation process of a complex intervention
(Medical Research Council, 2006, p.8)

3.3.1. Development

CIMT aims to effect change at the function or activity level (Novak et al., 2013; Sakzewski et al., 2009) and was considered suitable to target the affected upper limb in children diagnosed with HCP and therefore, presenting with activity limitation (Rosenbaum et al., 2007). A literature search on CIMT for the HCP population identified a Cochrane systematic review (Hoare et al., 2007). It included three trials (Deluca et al., 2006; Eliasson et al., 2005; Sung et al., 2005). These studies were critically appraised to inform the intervention design in combination with examination

of the presenting upper limb impairments and activity limitations in HCP. Furthermore, to generate hypothesis testing for the CATCH trial an underpinning theory was identified. The rationale for change in the affected upper limb as a result of CIMT is explained by motor learning theory. This is defined as relatively permanent change in the capacity for skilled movement associated with practice or experience (Schmidt and Lee, 2011, p.327). Two main paradigms of motor learning were considered and although the assumptions are different, the element of practice and activity to promote motor learning is key from both perspectives. The fundamental component, on which the interventions in the CATCH trial were modelled, was practice and activity with the affected upper limb. Once the upper limb interventions for the investigation were developed they were fully described guided by the Template for Intervention Description and Replication (TIDieR) checklist and guidelines (Hoffmann et al., 2014) developed by an international group of experts. This provided added assurance that the description was sufficiently complete for replication in the CATCH trial and for future investigations and implementation.

3.3.2. Feasibility and piloting

In order to guide piloting a sample size was calculated. This was based on existing evidence (Eliasson et al., 2005) and an attainable recruitment target. Expert advice was obtained for statistical aspects of the trial (see Appendix 2). Furthermore, feasibility of the CATCH trial was undertaken by evaluation of the recruitment and retention of participants and the acceptability of the trial procedures.

3.3.3. Evaluation

The effectiveness of the interventions administered in the CATCH trial were examined. A critical approach for intervention testing is the identification of reliable and valid outcome assessments to measure the outcome targeted by the intervention (Medical Research Council, 2006). The multilevel approach of the International Classification of Functioning, Health and Disability; (ICF, 2001) can be used to classify outcome measures according to their intended level of assessment. Therefore, to capture change in the CATCH trial an outcome measure was required which assessed activity. The ICF classifies the activity range using qualifiers, performance and capacity which can refine the choice of outcome measures further. Performance relates to what a person does in their actual environment and is observable and reflects functioning in a real life setting. Whereas capacity describes the best or highest practice (World Health Organisation, 2013). An expert consensus on CIMT (Eliasson et al., 2013) stated the goal of the CIMT intervention was to gain improvement of the upper limb performance, primarily of two-handed activities. Therefore, the primary outcome measured in the CATCH trial was bimanual performance. However, to ensure the effects were fully captured, outcome measures that asses both performance and capacity are required (Klingels et al., 2010) therefore, capacity was also measured.

Knowledge about the CIMT interventions from the parental perspective was considered important by an expert consensus (Eliasson et al., 2013). Therefore, a parent-reported motor outcome measure was incorporated in the assessment schedule in the CATCH trial. Furthermore, it is recommended in any healthcare

intervention that a more subjective understanding of the intervention effects should be included, rather than only the objective outcomes (Fayers and Machin, 2007). Hence, the effects of the interventions on the subjective perception of health using Health Related Quality of Life (HRQOL) assessments were measured.

To support a more accurate conclusion about treatment efficacy and inform replication in future studies, treatment fidelity measures which appraised the intervention delivery were included (Bellg et al., 2004). They evaluated the treatments in terms of what was actually delivered compared to what was intended (Carroll et al., 2007).

3.4. Rationale for trial design

A number of experimental research designs are available to test the effectiveness of the CIMT interventions such as pre-experimental designs (e.g. before-after-design with no control group) and quasi-experimental designs (e.g., non-equivalent control group). However, randomised controlled trials (RCTs) have been described as the most rigorous way of determining whether a cause-effect relation exists between treatments and outcomes (Sibbald and Roland, 1998).

In an RCT randomly formed groups are compared and can be assumed to be equivalent at the beginning. There are several important features of RCTs. These include;

- random allocation of participants to intervention groups which if concealed minimises selection bias,
- participants and investigators remain unaware (as far as possible) of group allocation,
- intervention groups are treated the same other than the intervention,
- patients are analysed within the group to which they were allocated (intention to treat analysis),
- the analysis focuses on estimation of the size of difference in predefined outcomes between the intervention groups (Sibbald and Roland, 1998).

To establish whether there is an association between the upper limb interventions administered in the CATCH trial and outcomes, a RCT was therefore the design of choice to reduce confounding and bias. Although other methodologies would be able to identify an association, factors influencing the outcome other than the intervention could not be ruled out. However, randomisation equalises groups at baseline on both known and unknown confounding factors. (Craig et al., 2008). The CATCH trial was a single blind, parallel randomised controlled trial. The features of an RCT listed have been implemented including: a randomisation methodology for group allocation, implementation of measures pre-randomisation to conceal allocation from the study personal and post-randomisation to blind the assessor to group allocation. Furthermore, an intention to treat analysis was conducted on pre-defined outcomes, on the difference in change scores between groups.

3.5. Trial methodology

3.5.1. Trial design

The CATCH trial was a parallel randomised controlled trial with blind assessment of the primary outcome measure.

3.5.2. Ethics approval management permissions, registration and substantial amendments

The trial was independently reviewed and subsequently recommended for ethical approval by South Birmingham Research Ethics Committee (22/June/2010; Reference 10/H1207/36). This favourable opinion was subject to management permission for research being obtained from the participating NHS research and development (R&D) offices from each NHS service. Furthermore, the University of Birmingham were approached and agreed to take on the role of study sponsors (09/07/2010). The study was assigned (15/06/2011) to the ISRCTN registry (ISRCTN 58484608). This is a primary clinical trial registry recognised by the World Health Organisation. It provides free accessibility links to the resulting publications (supports assessing publication bias and selective outcome reporting) and is kept up to date. Approvals are shown in Appendix 1

A substantial amendment (AMO1 16/12/2010) proposed a self-administered parent-questionnaire to replace a face-to face assessment at follow-up (24 weeks). This was in response to resource limitations as a result of extending recruitment nationally. A second substantial amendment changed the format and wording of the BBMQ to aid

readability and updated it from version one to version two (AMO2 07/02/2011). A third substantial amendment changed the prolonged restraint information packs. To enhance usability they were divided depending on whether the restraint used a wrist splints or a cast (AMO3 08/03/2011). Amendment approvals are shown in Appendix 1.

3.5.3. Study participants

The eligibility criteria for the trial are as follows and the rationale for them is discussed below.

Inclusion criteria

- Hemiplegic cerebral palsy (HCP)
- Aged 18 months to four years

Exclusion criteria

- HCP with a progressive aetiology
- Children with a medical condition that could cause an adverse reaction associated with the application of a plaster cast (e.g. eczema on the hands),
- Children who had had an episode of prolonged CIMT lasting two weeks or more in the previous six months.

The brain disturbance causing HCP may occur in the developing foetus or infant brain however, there is no explicit upper age limit specified, although the first two or

three years of life are considered most important in the timing of the disturbances (Rosenbaum et al., 2007). A distinction was not made between those children who had HCP as a result of a congenital or postnatal brain insult. However, cerebral palsy is defined as a non-progressive brain disturbance (Rosenbaum et al., 2007) therefore, children were excluded if the HCP was the result of progressive disease (e.g., a cerebral tumour).

HCP is a condition considered to be heterogeneous in terms of the neurological presentation and degree of motor disability (Johnson, 2002). The intervention under investigation in the CATCH trial has been developed for individuals with a unilateral disability but not for a specific neurological classification or degree of disability. Therefore, a complete range of presentations within the unilateral topography were included, which enhanced generalisability.

In cerebral palsy it is acknowledged there are often accompanying neurodevelopmental disorders present (e.g., epilepsy) in addition to the motor disability (Rosenbaum et al., 2007). This is a recognised part of the condition and did not lead to exclusion in the CATCH trial. However, if a child presented with a medical condition that could cause an adverse reaction when a cast was applied (e.g. eczema on the hands), they were excluded. Children with HCP would be expected to be receiving or have already received a number of health care interventions. This was acceptable for inclusion in the CATCH trial other than if they had had an episode of prolonged CIMT lasting two weeks or more in the previous six months because of possible carry-over. Queries about medical eligibility were dealt with by Dr Anne

Aukett (AA) a consultant paediatrician, who acted as the independent chair and medical expert on the Trial Steering and Data Monitoring Committee. See Section 3.14.1.

Pre-school children from 18 months to four years only were included in the CATCH trial. This age group was chosen because the intervention under investigation (CIMT with prolonged restraint) involved a short-term but permanent movement restriction of the unaffected upper limb. This may lead to difficulty with accessing the national curriculum. Children with HCP are already considerably disadvantaged by their motor and associated non-motor deficits. Therefore, it was considered unacceptable to add to this disadvantage by interfering with their education for an extended period of time. Additionally, schools may be unwilling to accept the added risks and demands imposed. It could also be argued that an intervention that has the potential to improve upper limb disability would be most useful before the challenge of compulsory education. Therefore, the upper age limit for inclusion in the CATCH trial was four years of age (i.e., nine months before the commencement of compulsory education). There is some variability across the UK in the compulsory school start age. In England and Wales, it is the term following the child's fifth birthday, in Scotland it is five years and in Northern Ireland four years (Eurydice Network, 2010). The lower age limit for inclusion in the trial was in line with the lower age limit for the selected outcome measures.

3.5.4. Settings

Initially the therapy departments of South Birmingham Primary Care Trust and an adjacent NHS trust (Sandwell Primary Care Trust) were approached and agreed to take part. Participant recruitment however, was more challenging than first envisaged. To achieve the sample size a Trial Steering and Data Monitoring Committee (see Section 3.14.1) advised to extend recruitment nationally (August 18th 2010). Appendix 4 includes the recruitment strategy. CATCH recruited from 16 NHS paediatric occupational and physiotherapy community services. A service consisted of one NHS trust however, there were instances where two trusts had combined and effectively offered a single service. One of the participating services was based in a paediatric outpatient department of a hospital and all others in paediatric community settings (i.e., children's centres, health centres or special schools). The interventions took place in the clinical setting or at the child's home or nursery.

3.5.5. Recruitment procedures

Pre-school children with HCP were recruited from the paediatric therapy treatment databases of participating therapy centres by their treating therapist. A diagnostic test for HCP is unavailable and instead diagnosis is based on clinical assessment (O'Shea, 2008). Potential participants were included if they had a confirmed diagnosis of HCP given by a medical consultant following a clinical assessment

3.6. Description of the trial interventions

A full description of the interventions administered in the CATCH trial was outlined according to the TIDieR guidelines (Template for Intervention Description and Replication; Hoffman et al., 2014; see Appendix 2).

3.6.1. Name of interventions

The interventions administered in the CATCH trial were called constraint induced movement therapy (CIMT). Prolonged restraint (a novel approach) was compared to usual NHS practice with manual restraint.

3.6.2. Intervention procedures

The interventions both provided one-hour per day of intensive practice for the affected upper limb offered intermittently by the parent/guardian or nursery worker and guided by an intervention therapist. At the same time the child's unaffected upper limb was restrained with one of two methods. CIMT with prolonged restraint used a more permanent restraint employing a non-removable cast/splint and bandage which was left in situ for a number of days and the manual restraint intervention used an intermittent manual holding technique.

3.6.2.1. Constraint induced movement therapy with a prolonged restraint

The intervention therapist made a non-removable short arm cast (above the wrist to the metacarpal-phalangeal joints) appliance for the unaffected upper limb. Or a standard short arm wrist splint was used. A bandage enclosed the hand and fingers once the wrist device was applied. Appendix 5 includes a copy of the instructions given to the intervention therapists for application and management of the restraint. This includes; how to make the cast, the setting for applications, duration of application and post removal an observational assessment of the immobilised upper limb.

Parents/guardians administered the intervention in the home environment. They were given guidance on; management of the appliance, on administration of intensive practice and completion of the daily diary. The information was given in writing in a home information pack (see Appendix 5). Throughout the intervention period the intervention therapist offered ongoing advice and guidance by telephone contact (a minimum of once a week) and fortnightly during face-to-face contact. The parents/ guardians were taught how to remove the device and could do so in an emergency. However, they were asked to contact the intervention therapist if it needed to be removed. It was considered that if the child knew it could be taken off by parents/guardians they would be more likely to request for this to happen.

3.6.2.2. Constraint induced movement therapy with a manual restraint protocol

In order to manage the intervention at home the parents/guardians undertook a clinic or home-based training session (one to two hours). This included administration of manual restraint of the unaffected upper limb, administration of intensive practice with the affected upper limb and completion of a daily diary. They were issued with a home information pack (see Appendix 5) which contained the relevant information. The intervention began on an agreed date after the training session. The intervention therapist advised and managed the restraint by a once a week telephone contact and once a fortnight face-to-face contact.

3.6.2.3. Materials used in the interventions

The cast was made from a semi-rigid casting tape (3M soft cast casting tape). This material is used commonly in musculoskeletal conditions. It offers a degree of immobility but unlike other casting material it can be unwound and therefore, easily removed. A synthetic padding was used to line the cast for added comfort. Some parents chose to apply a sock to the outside of the device. The wrist splint was a standard product with a palmar bar and velcro straps often used in musculoskeletal conditions to support or immobilise the wrist joint. The fingers were enclosed in a crepe bandage. In addition, the families used their own toys and if the intervention therapists decided that the parents/guardians did not have suitable toys at home, they could be provided for either group. No specific toys were identified but the intervention therapist would choose a selection from the Early Learning Centre Catalogue (2011). Written information packs were used and the home information pack is outlined in Appendix 5.

3.6.2.4. Constraint induced movement therapy in the nursery environment

Both methods of CIMT could be conducted in the child's nursery. If the nursery agreed to participate a training session was conducted with the relevant nursery staff. They were given a nursery information pack which contained the same information for each method of CIMT as the home information pack (see Appendix 5). The intervention therapist offered ongoing advice and guidance to the nursery either by telephone contact (a minimum of once a week) and fortnightly during face-to-face contact.

3.6.3. Intervention duration

The intervention duration was 42 days (six weeks) delivered usually in three separate two-week periods and completed within a ten week period. Between sessions either usual or no therapy (unrecorded) was conducted. To increase compliance there was flexibility around the duration of the intervention periods which could be negotiated between the family and the therapists' availability. It was advised that an intervention period should be no longer than 21 days. This decision was based on possible deterioration of the prolonged restraint device and informed by the patient, public involvement representative (JM).

The duration of the intervention was informed partly by usual clinical practice which offers discreet treatment packages of about six-week episodes. Furthermore, the studies (Eliasson et al., 2005; Deluca et al., 2006) included in the Cochrane systematic review (Hoare et al 2007), critiqued to inform the CATCH trial, offered

interventions of similar duration. The amount of hours of practice with the affected upper limb in the study by Eliasson et al. (2005) was 120 hours (two hours per day, two months). Similarly 126 hours (six hours per day for 21 days) was delivered in the investigation by Deluca et al (2006). It was considered that a similar amount of practice could be achieved in six weeks (three hours per day) with a non-removable restraint in situ in the CATCH trial.

3.6.4. Intervention fidelity

The amount of therapy delivered versus the planned intervention and the child's cooperation with the restraint was quantified by the parents/guardians and nursery workers. Two methods of parent and nursery reported outcomes were used. Firstly they recorded the interventions by completion of a daily diary provided in the information packs (see Appendix 5). This was collected by the intervention therapist usually at the fortnightly face-to-face contact. Furthermore, the parents/guardians and nursery workers provided the information in response to a weekly interview with the therapist using a questionnaire (see Appendix 5) .This was completed either over the telephone or face-to-face. The parent and nursery worker reported outcomes on fidelity to the treatment are discussed in Chapter 5.

3.6.5. Intervention therapists

Intervention therapists were either qualified paediatric physiotherapists or occupational therapists employed by the NHS. Additionally, all were members of their

professional organisation (Chartered Society of Physiotherapy or British Association of Occupational Therapy) and of the Health and Care Professions Council, the regulatory body of health care professionals. They had received the relevant NHS mandatory training. All therapists attended a basic introduction to Good Clinical Practice (GCP) delivered by the National Institute of Health Research (NIHR). This included training on the EU Directives, UK Regulations and Research Governance Framework requirements covering clinical trials. They undertook the CIMT intervention as part of their usual role and were not reimbursed for their activity either financially or with other incentives. They received one-to-one instruction from the author (PC) on the trial protocol. This included; a standardised face-to-face power point presentation, information on the application and management of the restraint device. A demonstration of the application was carried out where necessary. The therapists were not assessed on their standard of practice but were able at any time to contact PC for advice.

3.7. Outcome measures

3.7.1. Assessment time points

Baseline assessments were carried out prior to randomisation. This meant that assessment outcomes would not be biased by assessor knowledge of group allocation (Sedgwick, 2011). Outcome assessments were planned for immediately post-intervention at ten-weeks (70 days after the intervention start date), to assess the impact of the intervention. After this time the children returned to their usual therapy. Twenty-four weeks (168 days after the intervention start date) a follow-up

postal assessment was conducted (see Table 3.1.) This time point was informed by the study conducted by Eliasson et al. (2005) who used a similar follow-up time point (six-month post baseline assessment). The planned and actual assessments were recorded (i.e., baseline, ten-week and 24-week) and described with descriptive statistics (minimum, maximum, range, median and mean).

Baseline assessment (Face-to-face)	Randomisation	Intervention	Ten-week outcome assessment (Face-to-face) Blind assessor	Usual therapy	Follow-up 24-week (Postal)
• Assisting Hand Assessment • Quality of Upper Extremity Skills Test • PedsQL 4.0 Generic Core scales and 3.0 CP module or PedsQL Infant scale • Birmingham Bimanual Questionnaire			• Assisting Hand Assessment • Quality of Upper Extremity Skills Test • PedsQL 4.0 Generic Core scales and 3.0 CP module or PedsQL Infant scale • Birmingham Bimanual Questionnaire		• PedsQL 4.0 Generic Core scales and 3.0 CP module or PedsQL Infant scale • Birmingham Bimanual Questionnaire

Table 3.1. Assessment schedule, administration and time points

Assisting Hand Assessment (Krumlinde-Sundholm and Eliasson, 2003; Krumlinde-Sundholm et al., 2007); Quality of Upper Extremity Skills Test (Dematteo et al., 1992); PedsQL 4.0 Generic Core Scales (Varni et al., 1999) and; PedsQL 3.0 Cerebral Palsy (CP) Module for toddlers (Varni et al., 2006); PedsQL Infant Scales (Varni et al., 2011); Birmingham Bimanual Questionnaire (Trial specific)

3.7.2. Primary outcome measure.

Purpose of the primary outcome measure

The Assisting Hand Assessment (AHA; Krumlinde-Sundholm and Eliasson, 2003; Krumlinde-Sundholm et al., 2007) was selected as the primary outcome measure. It has demonstrated validity and reliability and was developed to measure and describe how effectively children aged between 18 months and 12 years with unilateral disabilities use their affected upper limb during bimanual performance. Importantly, this is a well-established tool which is frequently used in clinical practice (Krumlinde-Sundholm, 2012). Therefore, results from the CATCH trial could be more easily interpreted by clinicians and researchers and, syntheses more likely in meta-analysis.

The fundamental principle of CIMT is the provision of mass practice to the affected upper limb to improve functional activity by overcoming learned non-use or movement suppression (Taub et al., 1993; 1999). The theoretical framework underpinning the predicted improvement in activity as a result of CIMT is motor learning, defined as a change in skilled movement associated with practice (Schmidt and Lee, 2011). Both motor learning paradigms, discussed in the previous chapter could explain the improvement. Information processing (Adams' closed-loop and Schmidt's schema theories) predicts change because the effector (activator) of the pre-determined motor patterns is shifted towards the affected upper limb which allows refinement of the memory representation in the schemas. Conversely, from the dynamical and ecological (Gibson, 1988; Kelso, 1995) perspective, exploration of

the environment with the affected upper limb allows the spontaneously development of coordinated movement with the task and the environment.

To capture change associated with the CIMT interventions in the CATCH trial the selection of a primary outcome measure which targets the intended outcomes was required (Medical Research Council, 2006). Selection can be informed by the multilevel approach of the International Classification of Functioning, Health and Disability (ICF, 2001). The ICF can classify outcome measures according to their level of assessment and interventions by their intended outcomes (World Health Organisation, 2013). CIMT intends to improve functional activity or task execution (Novak et al., 2013; Sakzewski et al., 2009) therefore, an outcome measure assessing at the activity level (task execution) was required. The ICF can refine the choice of the outcome measure further, because it provided a means of classifying the scope of the activity, using the qualifiers performance and capacity. The former relates to what a person does in their actual environment and is observable and reflects functioning in a real life setting. Capacity describes the best or highest practice (World Health Organisation, 2013). An expert consensus on CIMT (Eliasson et al., 2013) stated that the primary goal of CIMT was to gain improvement in bimanual activity conducted in the usual or current environment therefore, a performance measure was required.

Bimanual skills are primarily targeted by CIMT because children with HCP rarely use their affected upper limb for unimanual tasks instead it is typically used when it is required, during bimanual tasks (Greaves 2010). It is these two-handed activities in

this patient group which typically may be compromised by amongst other factors, suppression of movement (developmental disregard) and require amelioration (Eliasson et al., 2013). Therefore, an assessment of bimanual performance was required as the primary outcome in the CATCH trial.

Klingels et al. (2010) conducted a systematic review of evaluative tools for individuals aged 2-18 years which assessed the upper limb at the activity level. Eighteen tools were identified and 11 met the inclusion criteria. Of those, two assessments (the Video Observations Aarts and Aarts (VOAA: Aarts et al., 2007) and the AHA measured bimanual performance of the affected upper limb. The AHA was chosen because as the primary outcome because it was more commonly used and had more validity testing (Klingels et al., 2010).

Administration

The AHA is conducted in two stages. Initially, the child takes part in a semi-structured play session which lasts about 15 minutes. The child sits at a table on a chair with the assessor on a chair opposite. A play session takes place with toys from the AHA KIT to facilitate bimanual activity (see Appendix 6 for a list of toys). The order that the tasks outlined in the scoring sheet are completed is flexible. It is video recorded with the camera pointing toward the palmar aspect of the affected upper limb. The assessment is scored at a separate time from the video recording. The AHA can only be conducted by an accredited AHA scorer which involves three days of training and

a follow-up assessment. A copy of the accreditation certification for PC can be seen in Appendix 6.

Scoring

The AHA consists of 22 items which are divided into; general usage (3 items), arm use (4 items), grasp-release (7 items), fine motor adjustment (3 items), coordination (2 items), pace (3 items). There is a 4-point criterion referenced rating scale (1-4), used to score each item of the AHA. A higher score represents better function (i.e., a score of 1 represents an ineffective action or one that is not performed, and a score of 4 indicates an effective action. A script of the AHA score sheet can be found in Appendix 6. The sum of scores may vary between 22 and 88 points and this raw score is also presented as a scaled percentage score. In addition, these ordinal level scores can be converted to an interval level (i.e., a logit scale using a conversion table) which allows parametric statistical analysis. As the logit scale ranges from negative to positive, it can be converted to a more user friendly scale, (i.e., logit-based 0-100 AHA unit scale; Krumlinde-Sundholm, 2012).

Missing data

The AHA is scored from the video footage taken of the assessment. If an action that is itemised on the score sheet is not performed by the child, a score of one (does not do) is achieved for that item. This is rather than the item categorised as missing. Therefore, the AHA should be completed for all items.

Psychometric properties

Construct validity was evaluated using a quantitative rather than a descriptive approach (i.e., a Rasch measurement model. Rasch,1960), which used probability estimates to order items and participants, concurrently along a continuum. The model ordered items from easiest to hardest, as well as individuals in terms of their upper limb abilities (based on the actual responses) on a common measurement line, with an interval unit (logit). Evidence for uni-dimensionality (i.e., a single construct) was demonstrated, as well as a satisfactory hierarchical scale structure. Additionally, the AHA was found to effectively discriminate between children with different ability to provide an appropriate range of ability measures with no floor or ceiling effects detected (Krumlinde-Sundholme and Eliasson, 2003).

Inter and intra-rater reliability of the AHA was investigated by Holmefur et al. (2009) and the inter-correlation coefficients (ICC) were found to be 0.97 (20 scores) and 0.98 (2 scorers). The intra-rater ICC was 0.99 when 20 scorers each rated one session on two separate occasions. In this investigation the standard error of the mean (SEM) was calculated (raw scores) for both inter and intra-rater settings. It was found to be 1.5 for inter-rater and 1.2 for intra-rater assessments, which gave error intervals of 3 for inter-rater and 2.4 for intra-rater raw scores. Therefore, excellent reliability was demonstrated for the AHA, although intra was slightly better than inter reliability.

3.7.3. Secondary outcome measures

Secondary outcome measure in the CATCH trial included:

- Quality of Upper Extremity Skills Test (QUEST; Dematteo et al.,1992)
- Health related quality of life (HRQOL) measures including

  Paediatric Quality of life Inventory (PedsQL) 4.0 Generic Core Scales (Varni et al., 1999) combined with PedsQL 3.0 Cerebral Palsy (CP) Module (Varni et al., 2006) for children two years or older

  PedsQL Infant Scales (Varni et al., 2011) for children less than two years.
- Birmingham Bimanual Questionnaire (BBMQ) a trial specific parent-reported motor questionnaire.

The purpose, administration, scoring missing data and psychometric properties for each measure will be described.

3.7.3.1. Quality of Upper Extremity Skills Test

Purpose of the outcome measure

The Quality of Upper Extremity Skills Test (QUEST; Dematteo et al., 1992) was developed for children with neurological impairment between 18 months and 8 years. The test evaluates unimanual functional tasks which the child is asked to perform rather than their usual practice therefore, classified as a test of best (capacity) unimanual skills (Klingels et al., 2010). An expert consensus on CIMT (Eliasson et al., 2013) recommended a measure of unimanual capacity as a secondary measure

because the activity practiced when CIMT is administered (restraint is in situ) focuses on unimanual skills. Therefore, unimanual capacity is likely to improve (Eliasson et al., 2013). Furthermore, the addition to the outcome schedule of an evaluation of capacity gives assurance that the change in activity (usual and best practice) was fully captured (Klingels et al., 2010).

Measures of unimanual capacity other than QUEST were available. A systematic review of evaluative upper limb tools at the activity level according to the ICF identified two other measures (Klingels et al. 2010). However, the Shriners Hospital for Children Upper Extremity Evaluation (Davids et al., 2006) was developed for older children (3-18 years) and the Peabody Developmental Motor Scales (Folio and Fewell, 2000) for children with developmental delay rather than neurological impairment.

The QUEST offered a means of evaluating upper limb capacity of the affected upper limb. However, QUEST also assesses the unaffected upper limb separately. The assessment of the unaffected upper limb provided a means of evaluating possible functional deterioration post-intervention as a result of immobilising the unaffected upper limb as part of the prolonged restraint intervention.

Administration

The test takes approximately 45 minutes to complete and involves facilitation of movement through verbal encouragement, toys, demonstration and/or handling the

child. The test is conducted in a quiet room in which the child can play on a mat on the floor and sit at a desk. The order that the tasks are completed is flexible. Items required for the testing are; four one inch blocks, a cup, paper and pencils, tiny objects and distraction toys. No formal training is required to administer this test.

Scoring

The affected and unaffected upper limbs were both scored. There are a total of 36 items divided into four domains which measure; dissociated movement, grasp, protective extension, weight bearing. The scorer gives a rating on hand function, ranging from 0 (poor) to 10 (good), a spasticity rating (none, mild, moderate, severe) and a cooperativeness rating (not, somewhat and very). Scores for each domain and a summary score were calculated. Higher scores represented a better quality of movement. The score was based on the child's ability to carry out an activity. Some items are divided into two responses (< half-range ≥ half-range) and others have a single response. The responses are either: achieved (2 points), not achieved (1 point) or not tested (0) therefore, a score entered for every item. Total and domain scores are calculated as percentages. A script of the scoring sheet can be found in Appendix 6.

Missing data

The QUEST assessment does include a score for items not tested to account for individual missing items. However, in accordance with guidelines from Dematteo et

al. (1992), if a complete domain of the test is not tested, then a score for that domain is excluded.

Psychometric properties

QUEST demonstrated concurrent validity (fine motor, 0.84) with the Peabody Developmental Motor Scales (PDMS-2; Folio and Fewell,2000), test-re-test ranged from 0.75-0.95 and observer reliability of the QUEST and its domains ranged from 0.51 to 0.96 (DeMatteo et al., 1993). Furthermore, a study conducted by Sorsdahl et al. (2008)**,** demonstrated intra-class correlation coefficients (ICC) which varied from 0.69 to 0.97.

3.7.3.2. Health related quality of life measures

Purpose of the outcome measures

It is recognised that intervention outcomes in clinical trials should not only include objective measurement of the assumed outcome but the effect of the interventions on the subjective perception of health (i.e., health related quality of life; HRQOL). A number of components can be included such as, the effect of the intervention on daily activities and emotional and social functioning (Fayers and Machin, 2007). Patient–reported assessment is often undertaken but, it is generally agreed that children younger than eight years are unable to partake (Ravens-Sieberer et al., 2006). Therefore, because of the age of the participants in the CATCH trial, parent-proxy HRQOL assessments were implemented. Selection of the measures was

based on: appropriate health condition, age range, and included dimensions that were perceived to have either a beneficial or be detrimentally affected, from the intervention. The PedsQL 4.0 Generic Core Scale was included whose generic nature meant it had the potential to identify the unintended consequences of the intervention (Craig, 2008). It was combined with a specific disease related module the PedsQL 3.0 Cerebral Palsy (CP) Module.

Description of the PedsQL 4.0 Generic Core Scale

The Paediatric Quality of Life inventory (PedsQL) measurement model was developed to integrate generic approaches to quality of life with disease-specific modules. The PedsQL 4.0 Generic Core Scales (Varni et al., 2001) was designed to measure HRQOL in healthy children and those with chronic conditions aged from two years to 18 years. The version for toddlers (2-4 years) was administered in the CATCH trial.

Administration

The PedsQL 4.0 Generic Core Scales was conducted as a parent-proxy assessment during a face-to-face interview at baseline and ten-weeks and as a postal questionnaire at the 24-week follow-up. It is a 21 item assessment form, which is divided into four dimensions; Physical functioning (8 items), Emotional functioning (5 items), Social functioning (5 items), Nursery functioning (3 items). A script of the PedsQL 4.0 Generic Core Scales can be found in Appendix 6.

Scoring

A 5-point response scale was used for both the PedsQL 4.0 Generic Core Scale. Parents/guardians were asked how much of a problem each item had been for their child over the previous month. Difficulty is categorised into; never (0), almost never (1), sometimes (2), often (3), almost always (4). None of the items were weighted. The items were reversed scored and linearly transformed to a 0-100 scale as follows; 0=100, 1=75, 2=50, 3=25, 4=0. Higher scores indicate better HRQOL A mean score for each dimension was calculated using the sum of the items over the number of items answered. Two summary scores were also computed. A Psychosocial summary score from the combined mean scores in the Emotional, Social and School functioning dimensions and a Total score from the mean scores on all the dimensions.

Missing data

If items were missing a mean score of included items was calculated. However, if ≥ 50% of items were missing from a dimension then it was excluded (Varni, 2010).

Description of the PedsQL 3.0 Cerebral Palsy (CP) Module

The PedsQL 3.0 CP Module (Varni et al., 2006), is a disease specific module developed to measure quality of life in children with cerebral palsy and designed to be combined with the PedsQL 4.0 Generic Core Scales.

Administration

It was administered at the same time as the PedsQL 4.0 Generic Core Scales as a parent-proxy assessment during a face-to-face interview at baseline and ten-weeks and as a postal questionnaire at the 24-week follow-up. The PedsQL 3.0 CP Module consists of 22 items and is divided into five dimensions; daily activity (5 items), movement and balance (5 items), pain and hurt (4 items), fatigue (4 items), eating activity (4 items). A script of the PedsQL 3.0 CP Module can be found in Appendix 6.

Scoring

Scoring of the PedsQL 3.0 CP Module was the same as the PedsQL 4.0 Generic Core Scales. The parents/guardians were asked how much of a problem each item had been for their child over the previous month. Difficulty is categorised into; never (0), almost never (1), sometimes (2), often (3), almost always (4). None of the items were weighted. The items were reversed scored and linearly transformed to a 0-100 scale as follow; 0=100, 1=75, 2=50, 3=25, 4=0. A mean score for each dimension was calculated using the sum of the items over the number of items answered.

Higher scores indicate better HRQOL. A summary score was not computed for the PedsQL 3.0 CP Module.

Missing data

If items were missing a mean score of included items was calculated. However, if ≥ 50% of items were missing from a dimension then it was excluded (Varni, 2010).

Psychometric properties of the PedsQL 4.0 Generic Core Scale and PedsQL 3.0 CP Module

Construct validity was demonstrated of the PedsQL 4.0 Generic Core Scale and PedsQL 3.0 CP Module for children with cerebral palsy (CP) by determining the difference in scores between healthy children and children with CP (Varni et al., 2006). Data was submitted to a t-test and a statistically significant difference was found on all dimensions and summary scores. Additionally, internal consistency reliability exceeded the minimal reliability standard of 0.70 required for group comparison for most of the scales and approached 0.90 for a number of scales (Varni et al., 2006).

Description of the PedsQL Infant Scale

The PedsQL Infant Scale (Varni et al., 2011) was developed to measure HRQOL for children between 13 and 24 months. It was used in the study for those children who

were younger than two-years. If the PedsQL Infant Scales was administered at baseline, it was recommended (email communication with author J. Varni) that the same version was administered at follow-up if the child was between 2 and 2.5 years. If at baseline, the child was nearly two years then the PedsQL 4.0 Generic Core Scale was administered.

Administration

The PedsQL Infant Scale is a 45 item parent-report form. It was conducted as a face-to-face interview with the assessor at baseline, and at the ten-week assessment. At the 24-week follow-up, the assessment was conducted as a postal questionnaire. The PedsQL Infant Scales consists of five dimensions; Physical functioning (9 items), Physical symptoms (10 items), Emotional functioning (12 items), Social functioning (5 items), Cognitive functioning (9 items). A script of the PedsQL Infant Scales can be found in Appendix 6.

Scoring

The parents/guardians were asked how much of a problem each item had been for their child over the previous month. Difficulty is categorised into; never (0), almost never (1), sometimes (2), often (3), almost always (4). None of the items were weighted. The items were reversed scored and linearly transformed to a 0-100 scale as follows; 0=100, 1=75, 2=50, 3=25, 4=0. A mean score for each dimension was calculated using the sum of the items over the number of items answered. Higher

scores indicate better HRQOL. A total score which included all items and a Psychosocial health summary score which combined the scores from the Emotional, Social and Cognitive functioning dimension were calculated. Additionally, a Physical health summary score was computed from the Physical functioning and Physical symptoms dimensions.

Missing data

If items were missing in the PedsQL Infant Scale, a mean score of included items was calculated. However, if ≥ 50% of items were missing from a dimension then it was excluded (Varni, 2010).

Psychometric properties

The validity of the PedsQL Infant Scale was supported by a statistically significant difference between HRQOL reported by parents of healthy children compared to parents of infants with health issues. The internal consistency reliability scales exceeded the minimum reliability scores of 0.70 required for group comparison (Varni et al., 2010).

3.7.3.3. Birmingham Bimanual Questionnaire

Purpose of the outcome measure

Gaining insight about interventions from the user perspective can provide invaluable understanding and contribution to evaluation of the CIMT interventions (Eliasson et al., 2013). In the CATCH trial because the participants were pre-school aged, the user perspective could only be provided from the parent/guardian. Therefore, a parent-reported motor outcome measure was included. This provided an oppurtunity to change administration of the 24–week follow-up assessment from a face-to-face to a postal questionnaire in response to resourse limitations because recruitment had been extended. A substantial amendment (AMO1 16/12/2010, see Appendix 6) proposed a self-administered parent-reported questionnaire be included in the assessment schedule and replace a face-to-face motor assessment at 24-week follow-up.

A suitable questionnaire for the purpose of the CATCH trial was not identified from a literature search. Therefore, the BBMQ was developed (the psychometric properties for the BBMQ are comprehensively reported in Chapter 7). The BBMQ is a parent-reported questionnaire. It evaluates assisting hand function in children with a unilateral motor impairment and can be administered as a face-to-face interview or self-administered. The BBMQ measured the effect of the intervention on change in bimanual function of the child's affected upper limb, from the perspective of parents/guardians immediately post-intervention and at follow-up.

Administration

The BBMQ is a six-item parent-reported assessment, which was administered as a face-to-face interview at baseline and 10-weeks and self-administered by parents/guardians at the 24-week follow-up assessment. A copy can be found in Appendix 6.

Scoring

A five-point Likert scale was developed which categorised the amount of difficulty a child had, according the parent/guardian, completing six upper limb tasks over the previous month. The scale ranged from; never had difficulty (0), almost never had difficulty (1), sometimes had difficulty (2), often had difficulty (3), almost always had difficulty (4). None of the items were weighted. The items were reversed and transformed to a 0-00% scale as follow; 0=100%, 1=75%, 2=50%, 3=25%, 4=0%. Therefore a higher percent represented better function. A mean score was calculated using the sum of the items over the number of items answered.

Missing data

If items were missing in the BBMQ, a mean score of included items was calculated.

3.8. Sample Size

In order to estimate how many participants are required to answer the research question, it is necessary to conduct a sample size calculation (Jones et al., 2003). Eliasson et al. (2005) conducted a non-randomised controlled trial of CIMT in young

children with HCP using the AHA as the primary outcome measure. The treatment effect for CIMT was 1.16 logits at the end of therapy (ten-weeks). It was considered that showing a similar effect at the end of treatment would provide sufficient justification to plan a larger trial to look at longer term outcomes and similar treatment effects. Therefore, the study was powered to detect a comparable treatment effect. It was calculated that a sample size of 23 in each group would have 90% power to detect an effect size of 1.0 logit following treatment, using a two group t-test with a 0.05 two-sided significance level. A total sample size of 60 makes allowance for withdrawals (see Appendix 3). The interventions investigated in the CATCH trial were predominantly administered by parents/guardians. This may have proved to be too to burdensome therefore, the sample size made allowances for withdrawals from the trial.

3.9. Randomisation and allocation concealment

In order to give reassurance that the intervention groups were the same at the beginning of the intervention, group allocation was conducted by a process of randomisation (Sibbald and Roland, 1998). It was managed and conducted by the Primary Care Clinical Trials unit (PC-CRTU) at the University of Birmingham which is an academic primary care facility for clinical trials in primary care and the community. To limit the effect that individual sites and therapists had on the outcomes, the randomisation was initially stratified by site and then participants individually randomised to either the prolonged or manual restraint group. To conceal the assignment sequence until group allocation had occurred, an unpredictable

assignment sequence was generated. This was a computer generated, balanced blocked randomisation schedule developed by a statistician independent of the trial, using nQuery Advisor 7.0 (Statistical Solutions, USA).

The schedule was held by the telephone randomisation service at PC-CRTU. Randomisation was conducted following baseline assessment. The local intervention therapist contacted the PC-CRTU by telephone using a unique code to identify the participant. The member of staff answering the randomisation call line was unaware of the participant identification and, assigned the participant according to the schedule. When the local intervention therapist made contact with the PC-CRTU for the purpose of randomisation, the assessor (PC) was not present either at the local site or at the PC-CRTU.

3.10. Blinding

The CATCH trial had a single blind design. It was not possible to blind parents/guardians, nursery workers or intervention therapists because of the nature of the intervention. The assessor (PC) was the only person blinded from group allocation. Blinding is imperative for treatment evaluation (Boutron et al., 2007) because unblinding can lead to assessment bias often resulting in an over estimation of results (Day and Altman, 2000). Therefore, to maintain blinding of the assessor a number of safeguards were put in place as recommended by the practical guidelines provided by Siemonsma and Walker (1997).

A particular issue was that PC had contact with a number of therapists by email and phone. Furthermore, she had direct contact with parents/guardians, intervention therapists and participants at the ten-week assessments. What is more, they were conducted at the venue where the research notes were held. Therefore, there was potential for unblinding. To safeguard blinding the parents/guardians were made aware verbally and where possible with a written reminder not to discuss group allocation in front of PC. Research notes were kept in a locked cupboard. Following two unintentional disclosures of group allocation by intervention therapist, a reminder not to disclose group allocation was left on the assessor's phone and email (10 Jan 2011).

Exposure to completed study documentation could have unblinded the assessor (PC). Therefore retrieval and recording did not include PC. The completed data collection sheets (daily diaries and parent questionnaires) were retrieved via post to the trial coordinators (TH, MF) and inputted onto a trial database by the research associate (AW). All trial information was recorded on an Access database, which was stored on the trial coordinators personal folder and password protected. Adverse events were initially reported to PC however, it was decided this could lead to un-blinding as they were associated with the prolonged restraint group. Therefore, this was discontinued (21 March 2011) and the trial coordinators (TH, MF) were contacted. Discussion about adverse events during the Trial Steering and Data Monitoring Committee (see Section 3.14.1.) was conducted in the absence of PC. Analysis of the data by PC did not commence until all outcome measures and data collection forms were returned and inputted onto the trial database and subsequently

locked (analysis began on September 20th 2012). Any instances of inadvertent un-blinding were recorded on the trial database by the trial coordinators (TH, MF).

In order to examine how effective the blinding had been an evaluation of blinding questionnaire was completed by PC at the ten-week outcome assessment time point. This time point was chosen because at the 24-week follow–up assessment, a parent-reported motor outcome measurement only was conducted who were aware of group allocation. The questionnaire was completed for each participant by PC and is presented in Table 3.2.

Table 3.2. Evaluation of unblinding

Participant ID	- - / - - -	
	Yes	No
Are you aware of the participant's group allocation?		
Indicate which group the child was allocated to	PR	MR
If yes, did you guess the allocation?		
If yes, were you inadvertently un blinded to group allocation?		

3.11. Flow of the participants through the trial

Once ethical approval was gained, the parents/guardians of eligible patients from the treatment databases of participating NHS paediatric services were approached by an intervention therapist (face-to-face / telephone). If they were interested in participating they were invited to attend a face-to-face session at the location where the child usually receives their therapy.

3.11.1. Informed consent

The age of the participants (18 months to four years) meant they were unable to provide consent therefore, parents/guardians were approached. They were given a full explanation of the trial by PC usually in the clinic setting. This included discussion about the treatment options and the manner of the treatment allocation. Furthermore, they received a Patient Information Sheet to read (see Appendix 7). Support from an interpreter was provided if required. Parents/guardians were given information about

the Patient Advisory Liaison Service (PALS) of Birmingham Healthcare Community Trust (BCHC), which is a confidential, advisory and support service for patients and their families. All parents/guardians (regardless of which NHS trust they were under) could contact PALS at BCHC to discuss the trial. They were provided with an information leaflet which included contact details (see Appendix 7). Furthermore, they were given the option to talk to a parent, whose child had previously received prolonged CIMT and in some cases given the option of viewing a DVD of a child receiving prolonged CIMT. Following the explanation parents/guardians were given at least 24 hours, to decide if they would like their child to participate in the trial.

3.11.2. Baseline assessment procedures

The baseline assessment schedule (see Table 3.1) was conducted as a face-to-face contact with the participant. PC, the intervention therapist and the parent/guardian were present. If necessary an interpreter was present. It took place in the setting where the child usually received their therapy. Information was gathered about the child by asking the parent/guardian and included; gender, ethnicity, date of birth, and if the participant attended a nursery.

The participant's medical notes or therapy notes were not available at the assessment therefore, could not be accessed but information was provided by parents/guardians. This might be expected to be less accurate than if extracted from the notes. Parents and guardians were asked about the cause of the child's hemiplegia however, children can have multiple risk factors for developing HCP (Eunson, 2012) which can make a definitive cause difficult to establish The results of

any neonatal scans and any other relevant medical conditions were also requested. The English Index of Multiple Deprivation (IMD) is an overall measure of deprivation. It combines: income, employment, living environment and crime for an area. The IMD was used to rank the relative level of deprivation of the participants using a conversion tool called GeoConvert (2006). Furthermore, to evaluate the residential area where the participant lived in terms of density of population an urban/rural score was used (five represents an urban area with a population of ≥ 10,000 (Office for National Statistics, 2010). The postcode of the participant's general practitioner (GP) was used for both the IMD and population density of residency.

The baseline assessments outlined in the schedule shown in Table 3.1 were administered by PC. This included the Assisting Hand Assessment (AHA; Krumlinde-Sundholme and Eliasson, 2003; Krumlinde-Sundholme et al., 2007) and the Quality of Upper Extremity Skills Test (QUEST; Dematteo et al., 1992). The parent/guardian was asked to read and complete two different questionnaires which they were given at the beginning of the face-to-face session. One was the Birmingham Bimanual Questionnaire (BBMQ) which takes approximately ten minutes to complete. If the child was two years or more the parent/guardian was asked to complete the PedsQL4.0 Generic Core Scales (Varni et al., 1999) and the PedsQL 3.0 Cerebral palsy Module for toddlers (Varni et al., 2006). If they were less than two years the PedsQL Infant Scales (Varni et al., 2011). The parent /guardian sat in the room with the child during the assessments and completed the questionnaires while the child was assessed, or when the assessments were completed (Appendix 6 for assessments).

3.11.3. Interventions and outcome assessments.

Following randomisation the interventions were administered in the clinic, the child's home or their nursery environment. The intervention duration was a total of six weeks delivered usually in three separate periods within a ten week period. The interventions were recorded by the parent/guardian and nursery worker.

At the end of the intervention period the ten–week assessment schedule (see Table 3.1) was conducted. After the assessment, the intervention therapists retrieved the daily logs from the parent/guardian and nursery worker and posted them with the parent and nursery worker questionnaires to the trial coordinators (TH, MF). The participants then returned to their usual therapy.

Twenty-four weeks from the start of the intervention period the parents/guardians, received a questionnaire by post (BBMQ, and HRQOL; see Table 3.1). The coordinating centre was responsible for sending out the questionnaire however, did not hold any identifiable information on participants. Therefore, in the first instance the questionnaires were sent to the intervention therapists. They were asked to forward them on to parents/guardians. They were completed and returned by post (stamped addressed envelope provided) directly to the University of Birmingham. It was requested that interpreters be provided if necessary and completed as a face-to-face contact. A second 24-week assessment was posted out, if the first was not returned within approximately six weeks. If the second assessment was not returned, telephone contact was established and an offer to complete the assessment over the telephone was made.

To prompt a return of the postal questionnaire an incentive (£10:00 gift voucher) was offered to parents/guardians on return of the 24-week assessments. As consent to participate in the study had already been received this was considered an acceptable practice by the research ethics committee. Once the 24 week assessment was completed the participant's involvement in the study then ended. Parents/guardians of participants randomised to the manual restraint group who wanted their child to receive an episode of the prolonged restraint, were offered this intervention after the 24-week follow-up assessment however, this was not recorded.

3.12. Data management

3.12.1. Data storage and management

A Microsoft Access database was created and used to manage all trial data. This included; the demographic data, outcome assessments, adverse events, eligibility queries, unblinded cases and data on fidelity to treatment. Data was stored on the password protected trial database. Data entry was carried out by a research assistant (AW) on a password protected drive with restricted user access, hosted by the Department of Primary Care Clinical Sciences at the University of Birmingham (UoB). The Information Technology (IT) service at the UoB ensured data were backed-up.

3.12.2. Data cleaning

Prior to analysis a process of data cleaning was conducted to check for inaccurate or incomplete data. The demographic data were checked and if data were missing, local sites were contacted to complete the data. Pragmatically, thirty percent of randomly selected assessments on the electronic access database were compared with paper copies. Any errors were corrected. In response to a large number of errors on the QUEST assessment, it was decided to check 100% of them with paper copies. Furthermore, if following analysis there were any extreme values the data were trawled to identify incorrect entries. Randomly selected diaries (10%) on the electronic database were compared with the paper copies. It was not always clear which day of the intervention period the data in the diaries referred to, therefore, in some instances the nursery was directly contacted.

3.13. Data analysis

3.13.1. Missing data

Assessments were examined for missing data and handled in accordance to each author's original instructions. For QUEST if a complete subscale was not tested it was excluded from the analysis. In addition, health related quality of life assessment (PedsQL4.0 Generic Core Scale, PedsQL 3.0 CP Module and the PedsQL Infant Scale) dimensions were excluded if they were less than 50% complete.

3.13.2. Data analysis

Analysis began once the ten-week and 24-week assessments had been returned and inputting onto the Microsoft Access database, had been completed. The database was subsequently locked. The data analysis began afterwards on September the 20th 2012. An intention to treat analysis was conducted. Therefore, all participants recruited to the trial as far as possible were analysed and their outcome measures compared according to the group to which they were allocated. This analysis was adhered to even if the participant did not start the allocated intervention, subsequently withdrew, or diverged from the intervention protocol. The aim was to minimise potential confounders by maintaining the similarity of baseline characteristics between groups and reflect what is likely to happen in clinical practice (Sedgwick, 2014).

Prior to analysis various distributions of the data were examined to check that the required assumptions of the planned analysis were met. This included normality assessment which was undertaken through visual examination of frequency distributions with histograms and z-scores for skewness (scores < 1.96 were assumed to be unimportant and normally distributed).

The baseline characteristics were compared across groups to determine the similarity and evaluate how effective randomisation had been (Sedgwick, 2014). Subsequently descriptive analysis for both intervention groups was completed using numbers and percentages for categorical variables and means and standard deviations for continuous variables. The dispersion of values was examined across groups using

box plots which allowed comparison of the spread of data in terms of quartiles, and possible outliers (Field, 2009).

A comparison between planned and actual assessment timings was conducted using descriptive statistics and the distributions across groups compared using boxplots. A non-parametric analysis using a Mann-Whitney U test was conducted to compare the difference in timings across groups

The groups were compared using an a prior primary outcome (ten week assessment) on the change in bimanual performance measured with the Assisting Hand Assessment (Krumlinde-Sundholme and Eliasson, 2003; Krumlinde-Sundholme et al., 2007). Furthermore, the change across groups on the pre-specified secondary outcomes was measured using; the Quality of Upper Extremity Skills Test (Dematteo et al., 1992), PedsQL 4.0 Generic Core Scales (Varni et al., 1999), PedsQL 3.0 Cerebral Palsy Module (Varni et al., 2006), PedsQL Infant Scales (Varni et al., 2011). A parent-reported motor outcome tool the Birmingham Bimanual Questionnaire (BBMQ) (introduced post study start) was also included.

Between group comparison of the primary and secondary outcomes were computed at the ten-week outcomes and the secondary outcomes (except QUEST) at the 24-week follow-up. Interval data were analysed across groups with independent t-tests. The assumptions required for the t-test (variance is roughly equal, scores are independent and normally distributed; Field, 2009) were examined. Confidence intervals were presented where useful. Categorical data were analysed with

Pearson's chi-squared test (χ^2). If the outcome from the analysis resulted in a p-value of < 0.05 the null hypothesis of no difference was rejected. Within group comparisons at baseline and ten-week assessments were made using dependent t-tests. Effect sizes were calculated where appropriate using Pearson's correlation coefficient (r) and reported and designated as small (0.20), medium (0.50) and large (0.80; Cohen, 1988).

In order to measure the effect of possible confounding variables on the primary outcome a regression analysis was conducted. The independent variables that may affect the score were identified based partly on theoretical reasons and partly on clinical reasoning. Furthermore all of the variables were included in a multiple regression model and a backward stepwise method used to calculate the contribution of each variable using the significance value of the t-test (Field, 2009).

3.14. Research governance

3.14.1. Trial Steering and Data Monitoring Committee (TSDMC)

An independently chaired combined TSDMC was appointed. The role of the data monitoring committee was included in the trial steering committee because the intervention was not invasive and had perceived low risk of adverse events. Dr Anne Aukett (AA) a medically qualified, highly experienced consultant paediatrician acted as the independent chair. The members and their roles are outlined in Appendix 8. The committee met before recruitment began on the 18/08/2010 and then every 3-6 months. The final TSDMC was held on the 18th of February 2013. The progress of

the trial was monitored and the committee provided advice on data monitoring and the conduct of the trial. AA acted as the medical expert for the trial. Queries regarding inclusion were referred to her as were serious adverse events for assessment of causality as soon as the trial team became aware of them. The patient, public involvement representative (JM) was a member of the TSDMC.

3.14.2. Risk assessment

Careful consideration of consequences of the intervention and measures to minimise the risks were made. The potential harm or risk to the participants can be assessed according to the characteristic of the risk, including the probability of it occurring, its magnitude and duration (Royal College of Paediatrics and Child Health, 2000). The foreseeable risk of the intervention was estimated as low. It was expected the participant may object initially (i.e., an infant is likely to withdraw in response to any stimulus (Council for International Organisations of Medical Sciences and World Health Organisation, 2002). However, if the objection continued over a period of two to three days, then this was reviewed by the parent/guardian and intervention therapist and potentially terminated. Furthermore, an intervention therapist conducted an observational assessment immediately following every episode of restraint of the unaffected upper limb, to monitor any side-effects. This was important especially in light of possible subtle functional deficits already present in the unaffected upper limb in the child with HCP (Steenbergen and Meulenbroek, 2006).

Serious adverse events were reported to the University of Birmingham who acted as the study sponsor (see Appendix 1) and local NHS R&D offices were informed. The

events were reviewed by the TSDMC (excluding PC to prevent unblinding). Furthermore, twelve monthly progress reports were submitted to the NHS Research Ethics Committee. If evidence of harm to the child or family emerged during the trial as a result of the research then the interest of the child would be paramount (Medical Research Council, 2004) and appropriate action taken.

3.14.3. Information governance

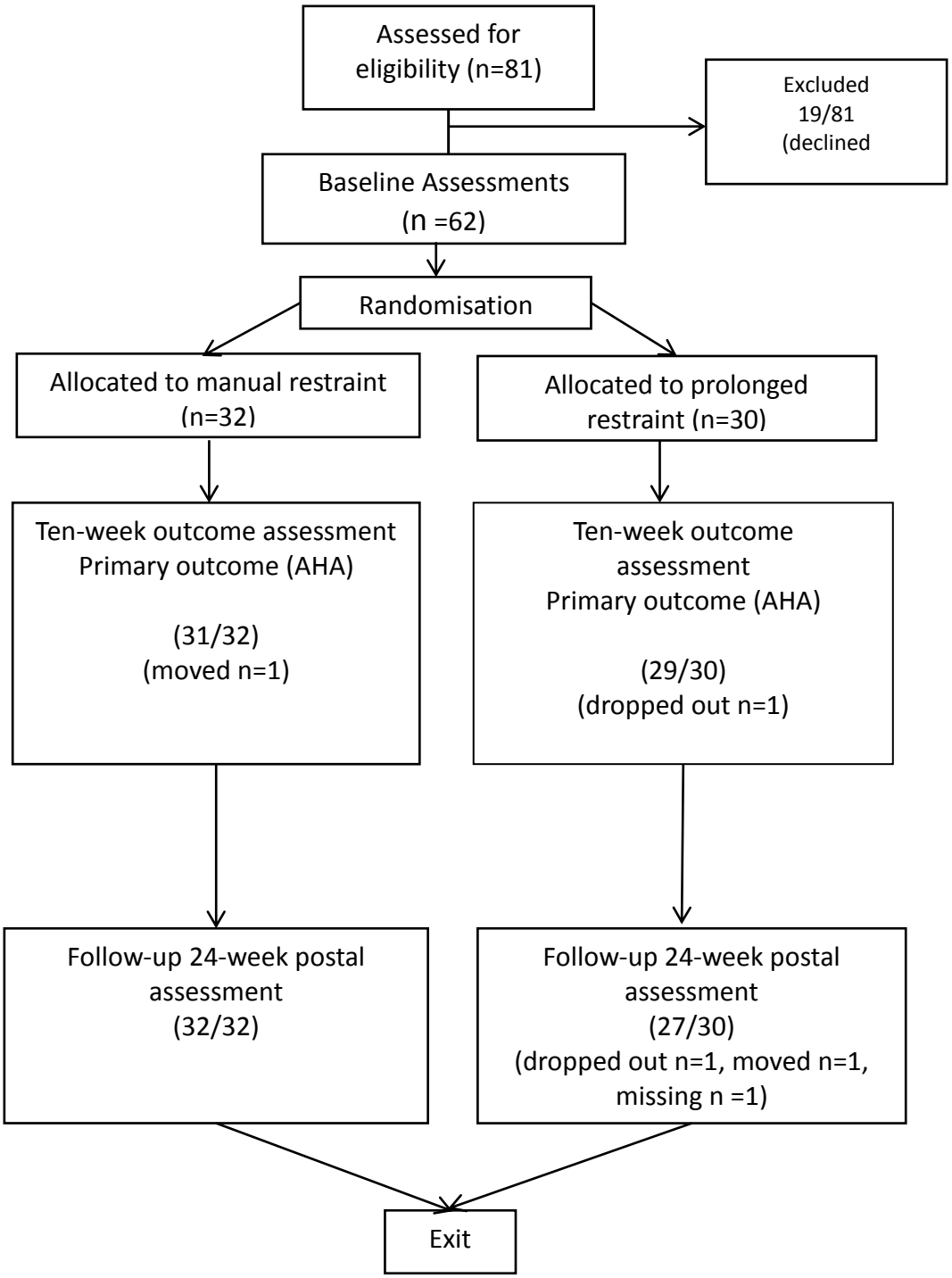
No patient identifiable information was used in the CATCH trial. A DVD was made as part of the AHA assessment of the participant. In order to ensure confidentiality the DVD was encrypted to the standard recommended by the NHS. The NHS information governance data encryption algorithms applicable at the time were 1) 3 DES (168bit) 2) AES 256 3) Blowfish with a minimum key length of 256 bits (Department of Health, 2008). The research data were kept in secured filing cabinets/drawers at the local NHS sites or on a password protected data base at the University of Birmingham.

Chapter 4: Results of the CATCH trial

4.1. Participants' flow through the trial and data collection

4.1.1. Participants' flow through the trial

In accordance with the updated CONSORT statement (Schulz, 2010) and the CONSORT statement extension to include non-pharmological trials (Boutron et al., 2008) a diagram of the flow of participants through the trial is shown in Figure 4.1. It includes participant screening, recruitment, intervention allocation, levels of attrition and analyse of the primary outcome.



Assisting Hand Assessment (AHA)

Figure 4.1. CONSORT flow-diagram

4.1.2. Screening and recruitment

This was a multicentre trial which initially recruited from two NHS community paediatric therapy services. Research and development (R&D) approval was gained (August 11th 2010) for both sites (South Birmingham, Sandwell). Participant recruitment however, was more challenging than first envisaged. To achieve the sample size, recruitment was extended (August 18th 2010) and children were recruited from a total of 16 NHS community paediatric therapy services. The recruitment period was between August 2010 until January 2012 by 26 physiotherapists and four occupational therapists. Those services included in the trial were geographically located across England and Wales in; Birmingham (two separate sites, South Birmingham, Heart of England), Dudley, South Staffordshire, Wolverhampton, Sandwell, Devon including South Devon, Walsall, London (three separate sites; Lewisham, Homerton Bromley), Shropshire, Telford and Wrekin, Leicestershire, Liverpool, and Powys. See Appendix 1 for R&D approvals.

The first participant was consented on the 13th December 2011. Eighty one parents/guardians of eligible children were approached. Consent for participation was given for 62 children and sites recruited between one and four participants except South Birmingham which had 19 participants. The reasons given for non-participation varied. Concerns about the child were given by a number of parents/guardians. This included the child's behaviour (n=2), child's independence (n=2) and the child's health (n=3). Also two children already attended an educational placement which was the reason given not to participate. Furthermore, the family stated they already

attended a number of hospital appointments or have other commitments (n=2) therefore, they did not want to consent. Two parents were not happy with the intervention and one did not want to participate in a research project. A number of parents/guardians did not give a reason for non-participation (n=5).

Table 4.1. Eligible participants approached and reasons for non-participation.

Site	Invited (n=81)	Consent provided (n=62)
South Birmingham	21	19
Heart of England	1	1
Dudley	7	3
South. Staffordshire	4	3
Wolverhampton	5	3
Sandwell	4	3
Devon	4	4
Walsall	2	2
Lewisham	5	2
Homerton	5	4
Bromley	5	3
Shrophire	2	2
Telford and Wrekin	3	3
Leicestershire	5	4
Liverpool	4	4
Powys	3	2

4.1.3. Group allocation and attrition

Of the 62 participants recruited, 30 were allocated to the prolonged restraint group and 32 to the manual restraint group. At the ten-week assessment one from each group was not assessed. In the prolonged restraint group a total of three were not assessed at the 24-week follow. In the manual restraint group all participants were assessed at 24 week follow-up. The participant not assessed at ten-weeks had moved area before the assessment but continued on the trial and completed the 24-week postal assessment.

4.1.4. Actual versus planned assessment time-points

The baseline assessment was planned to be conducted prior to randomisation and the ten-week assessment immediately after the intervention ended (70 days after the intervention start date). The 24-week follow-up assessment was intended to be carried out 168 days from the intervention start date. The ten-week assessments were actually carried out near to the proposed time point. The mean (SD) time from intervention start was 72 (6) days. One assessment was 32 days late. There was a greater difference between planned and actual time for the 24-week follow-up assessments. The mean (SD) time of actual assessments was 191 (40) days from the intervention start and substantially more than the planned 168 days. This may have been expected because it was a postal rather than a face-to-face questionnaire. A comparison of the actual and planned assessment time points across groups is shown in Table 4.2. The box-plots in Figure 4.2 demonstrate the distribution of the difference between actual and planned outcome assessments across groups. The

interquartile ranges (IQR) at 10-weeks indicate little dispersion with one very late case in the manual restraint group. However, the IQR at the 24-week follow-up assessment in the prolonged restraint group appeared more dispersed with more cases with late assessments, than the manual restraint group. However, the group medians of the difference in the timings of the 24 week assessments were compared (U=.336, p=.250) and were not statistically significant different.

Table 4.2. Actual timings of assessments relative to the proposed timings

Timing (days)		Ten-week assessment	24-week assessment
Planned		70	168
Actual	Median	71	175
	Minimum	60	134
	Maximum	102	357
	IQR (25%)	70	168
	IQR (75%)	74	207
	Mean (SD)	72 (6)	191 (40)

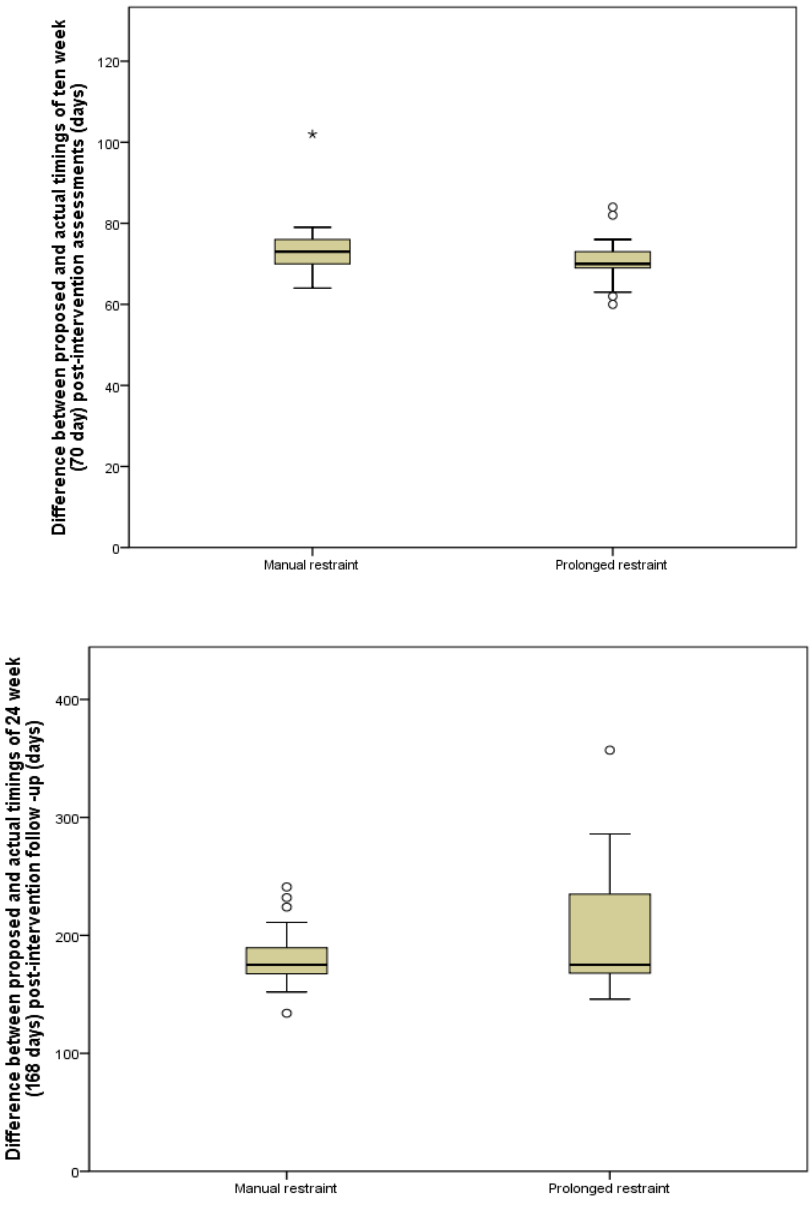


Figure 4.2. Difference between actual and planned outcome assessment time points across groups

4.1.5. Evaluation of assessor blinding

The assessor (PC) in the CATCH trial was blind to group allocation. The success of the blinding procedure was evaluated by the completion of a questionnaire by the assessor which included four items (see Figure 3.2.). It revealed that group allocation was known for five cases (5/60). Of the five cases, group allocation was revealed in three and PC correctly guessed in two cases.

The unintentional un-blinding (n=3) was a result of the intervention therapists or parents/guardians accidently informing PC about the group allocation. One of the participants was allocated to the prolonged restraint group and the other two to the manual restraint group. Furthermore, PC correctly guessed allocation for another two cases (one in the prolonged and one in the manual restraint group). One guess was based on the child attending the ten-week assessment with a bruise on their forehead and PC assumed this was because they had fallen and been unable to save themselves because a restraint was in place. In another case, a comment made by a parent/guardian led PC to believe the child was probably in the manual restraint group. The flow chart in Figure 4.3 outlines assessor knowledge of group allocation at the ten-week assessment.

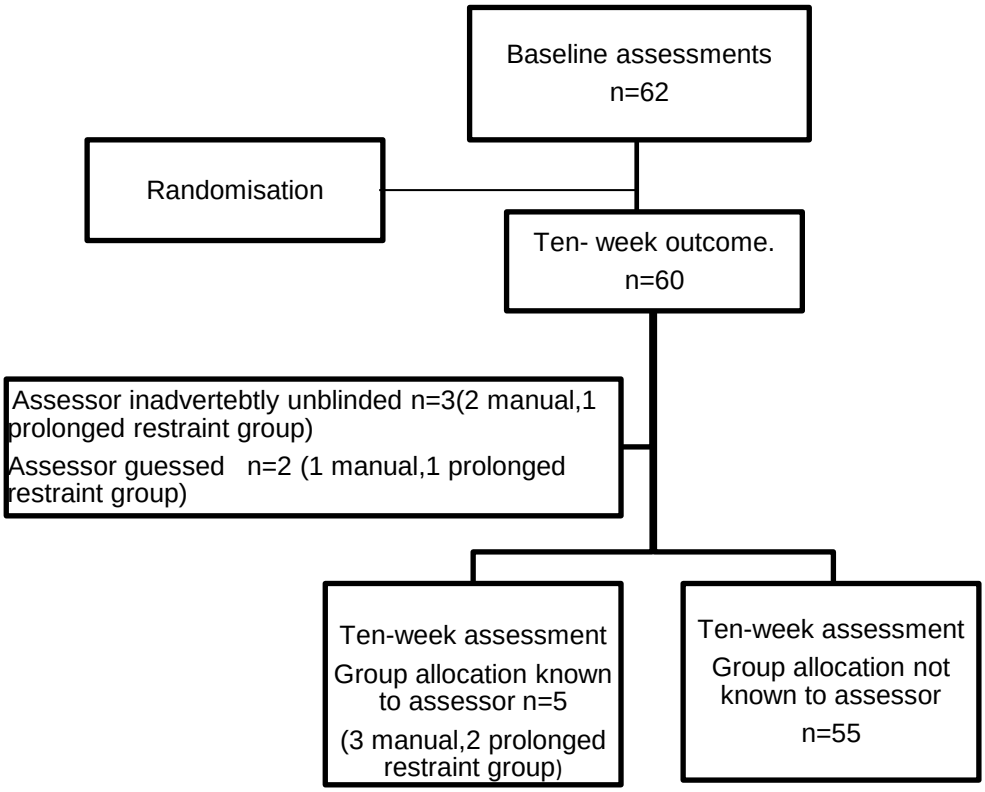


Figure 4.3. Flow chart of the assessor's knowledge of group allocation of participants at the ten- week assessment

4.1.6. Response rates and missing data

The data was uploaded and cleaned before the database was locked on September 20th 2012 after which time data analysis began.

4.1.6.1. Primary outcome assessment: Assisting Hand Assessment

The Assisting Hand Assessment (AHA; Krumlinde-Sundholm et al., 2007;Krumlinde-Sundholme and Eliasson, 2003) was completed at baseline and the ten-week assessment by PC. All 62 assessments were completed at baseline and only two assessments were not available at the ten-week assessment. Therefore, 97% (60/62) were completed. The AHA assessments had no missing items.

4.1.6.2 Quality of Upper Extremity Skills Test

The Quality of Upper Extremity Skills Test (QUEST; Dematteo et al., 1992) was completed at baseline and the ten-week assessment by PC. Sixty-two were completed at baseline and 60 were completed at the ten-week assessment which represents a 97% return rate. All domains were completed other than seven cases of the protective extension domain at baseline and a further four at the ten-week assessment. In addition, one weight bearing domain was not completed at the ten-week assessment.

4.1.6.3 Health Related Quality of Life

At baseline, two (2/51) of the PedsQL4.0 Generic Core Scale (Varni et al., 1999) and PedsQL 3.0 Cerebral Palsy (CP) Module (Varni et al., 2006) combined questionnaires were missing. Furthermore, at both the ten-week assessment and at the 24-week assessment three (3/51) combined questionnaires were missing. There were two cases at the 24-week assessment where one of these combined questionnaires were missing. There were no PedsQL Infant Scale (Varni et al., 2011 questionnaires (n=11) missing at any-time points. There were four cases where there was inconsistency in the questionnaire administered. PedsQL 4.0 Generic Core Scale and the PedsQL Infant Scale were both administered in these cases at different assessment times. These cases were excluded. The missing and inconsistent (mismatched) questionnaires across assessment time points are listed in Table 4.3

.

Table 4.3. Identifying missing and mismatched HRQOL assessments at each time point

	Baseline	ten-week Assessment	24-week Assessment
Missing questionnaires			
Case	GSS and CPM	GSS and CPM	
Case		GSS and CPM	GSS and CPM
Case			GSS and CPM
Case		GSS and CPM	
Case	GSS and CPM		
Case			GSS and CPM
Case			CPM
Case			GSS
Mismatched questionnaires (administered questionnaire listed)			
Case	ISS	ISS	GSS
Case	GSS	ISS	GSS
Case	GSS	ISS	GSS
Case	ISS	ISS	GSS

PedsQL 4.0 Generic Score Scales (GSS), PedsQL 3.0 Cerebral Palsy Module (CPM),PedsQL Infant Scale (ISS)

Missing data was handled in accordance to the author instructions (i.e., if < 50% of a dimension was completed it was excluded; Varni, 2010). Most dimensions have been included, except the nursery dimension of the PedsQL 4.0 Generic Core Scale where a number of cases (n=31) across the three assessment time points (baseline n=13, ten-week assessment n=11 and 24-week assessment n=7) were excluded. Furthermore, the PedsQL 3.0 CP Module had a number of dimensions (n=6) excluded at the ten-week assessment. Two cases had the daily activities dimension excluded, two had the pain and hurt dimension excluded, one had the fatigue dimension excluded and one the movement and balance dimension excluded. The PedsQL Infant Scale had one case with two dimensions missing at the ten-week assessment. They were the social and cognitive dimension. The excluded dimensions from each assessment at each time point are shown in Table 4.4.

Table 4.4. Excluded dimensions in the HRQOL assessments across time points.

Questionnaire dimensions	Baseline	Ten-week assessment	24-week assessment
PedsQL 4.0 Generic Core Scale			
emotional functioning			
social functioning			
nursery functioning)	13	11	7
physical functioning			
PedsQL 3.0 CP module			
daily activities		2	
movement and balance		1	
pain and hurt		2	
fatigue		1	
eating activities			
PedsQL Infant scale			
physical functioning			
physical symptoms			
emotional functioning			
social functioning		1	
cognitive functioning		1	

There were a number of dimensions that had missing items but the dimensions were more than 50% complete and therefore included. Table 4.5 shows the questionnaire dimensions that have missing items at each time point.

Table 4.5. Missing items in the HRQOL assessments shown across time points.

Questionnaire dimensions	Baseline assessment (n cases)	Ten-week assessment (n cases)	24-week assessment (n cases)
PedsQL 4.0 Generic Core Scales,			
emotional functioning		2(2)	1(1)
social functioning			1(1)
nursery functioning)			
physical functioning			1(1)
PedsQL 3.0 CP module			
daily activities		2(13)	
movement and balance			
pain and hurt		1(4)	
fatigue			
eating activities		4(1)	
PedsQL Infant scale			
physical functioning			2(2)
physical symptoms			
emotional functioning	2(2)	1(1)	1(1)
social functioning		3(3)	
cognitive functioning	4(3)	1(1)	

4.1.6.4. Birmingham Bimanual Questionnaire (BBMQ)

The BBMQ was completed by parents/guardians at baseline, ten-week assessment and at the 24-week assessment. The BBMQ was introduced after the CATCH trial had begun and eight participants had already carried out baseline assessment, therefore, those parents/guardians did not complete the BBMQ. Furthermore, the BBMQ was adapted in response to user feedback and a more user friendly version (two) was introduced. The participants (n=4) that had completed version one were excluded. Fifty BBMQ questionnaires from baseline were included in the analysis. At the ten-week assessment all questionnaires except two (60/62) were returned and all except three (59/62) at the 24-week assessment. Some participants had questionnaires missing from more than one time point. There were no missing items at any time points other than one questionnaire had one item missing at baseline.

4.2. Participant characteristics at baseline across groups

The age of the children across groups was similar (p = .427) with a mean (SD) age of 31.5 (12.2) months in the prolonged restraint group and 29.0 (11.8) months in the manual restraint group. Furthermore, the gender of the children was the same (p = .125) with 63% (19/30) of boys in the prolonged restraint group and 41% (13/32) in the manual restraint group. In addition, there was no group difference on ethnicity (p = .284) between groups with 33% (10/30) of the prolonged restraint group and 50% (16/32) of the manual restraint group classified by their parent/guardian as other than White British. The range and the distribution of participant ethnicity across groups, is

shown in Figure 4.4. An almost equal proportion (40%) of children attended nursery in each group (mean group difference p = .100). The QUEST outcome measure at baseline was used to gage the child's level of cooperation and there was no difference across groups (p = .346) in the number of children categorised as uncooperative (i.e., 40% in the prolonged restraint group and 29% in the manual restraint group). The English Index of Multiple Deprivation (IMD; 2010) was used to rank the relative level of deprivation of the area in which the participants lived (based on the General Practitioner postcode). The scores were compared across groups and there was found to be no difference (p = .326). The baseline characteristics and comparison across groups of the participants are shown in Table 4.6.

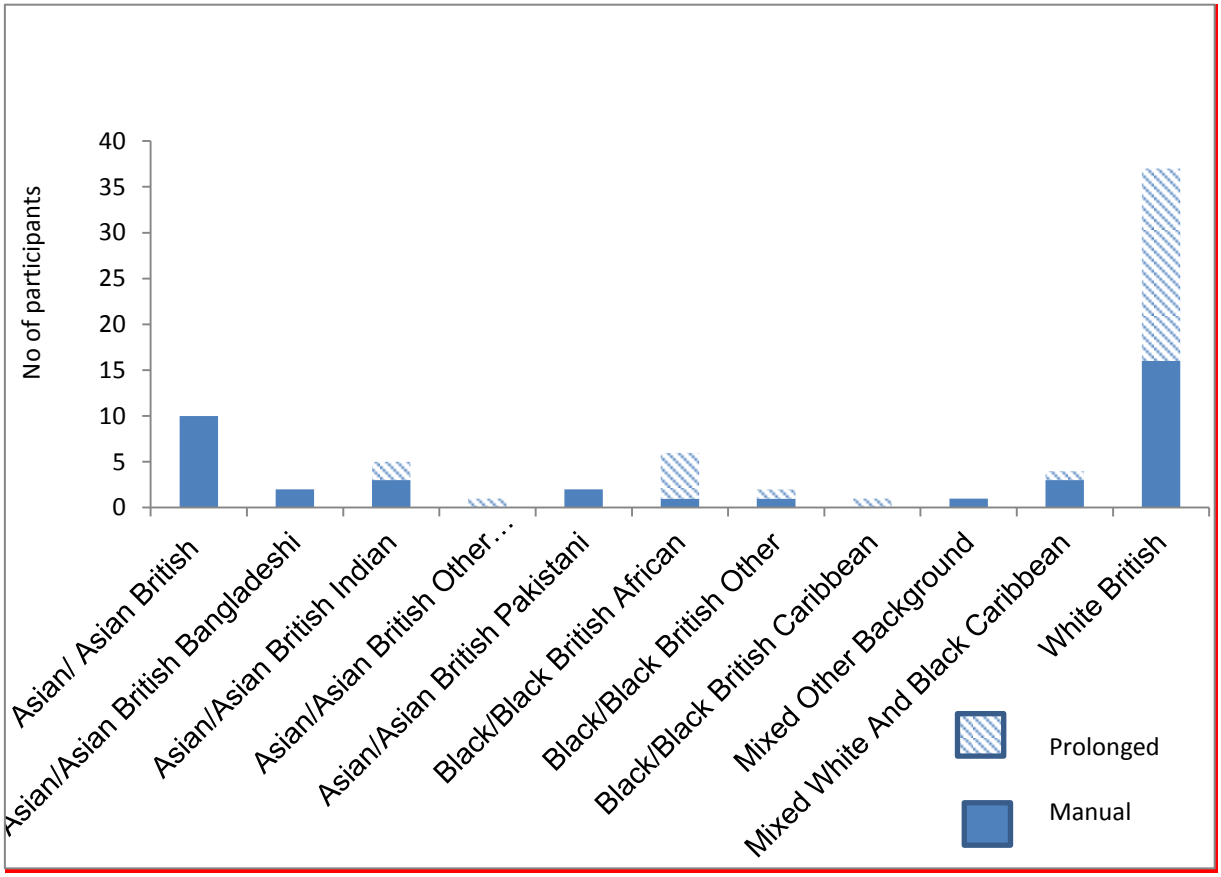


Figure 4.4. Ethnicity frequency across group

Table 4.6. Baseline characteristics and comparison across groups

	Prolonged restraint	Manual restraint	p-value
	Mean (SD)	**Mean (SD)**	
Age(months)	31.5 (12.2)	29 (11.8)	p=.427
Deprivation scores. (2 cases missing live in Wales not available)	9975.5 (8357.3)	7941.3 (7557.6)	p=.326
	n (%)	**n (%)**	
Gender			
Male	19 (63)	13 (41)	p=.125
Female	11 (36)	19 (59)	
Ethnicity			
White British	21 (66)	16 (50)	p=.284
Other	10 (33)	16 (50)	
Attends nursery			
Yes	12 (40)	13 (41)	p=.100
No	18 (60)	19 (59)	
How cooperative QUEST			
Not cooperative	12 (40)	9 (29)	p=.346
Somewhat cooperative	13 (43)	12 (39)	
Very cooperative	5 (17)	10 (33)	

4.2.1. Aetiology of hemiplegic cerebral palsy across groups

Prematurity is a common risk factor associated with CP (Eunson, 2012) and was given by 13% (8/62) of parents/guardians as the cause of their child's hemiplegia. However, this amount could have been higher as a number of the descriptors used by parents/guardians such as intra-ventricular bleed could also be associated with prematurity. Aetiology was not provided by all parents/guardians and it was easier for parents/guardians to pinpoint a post-natal event such as a sickle cell crisis.

4.2.2. Participant co morbidities across groups

A number of co-morbidities were reported by the parents and guardians. In the prolonged restraint group, 40% (12/30) were reported to have co-morbidities and 25% (8/32) were reported in the manual restraint group. Co-morbidities such as broncho-pulmonary dysplasia are associated with prematurity (Northway et al., 1967) and thus not unexpected. As previously discussed, it is recognised that the motor impairment of cerebral palsy can be accompanied by other impairments such as epilepsy (Rosenbaum et al., 2007). An unexpected co-morbidity was Down's syndrome which presented in two participants, both randomised to the prolonged restraint group.

4.2.3. Baseline measures

4.2.3.1. Assisting hand Assessment (AHA)

Sixty two participants were measured at baseline with the AHA and the difference across groups was examined using independent t-tests. The mean difference was -.89 (95% CI: -12.4, 14.1, p = .894) logit-based 0-100 AHA-units and not statistically significantly different. Baseline means and the difference in means across groups is shown in Table 4.7.

Table 4.7. Mean difference of the logit-based 0-100 AHA-unit score across groups at baseline

	n	Mean(SD) baseline	95% CI Lower	95% CI Upper	Difference in mean across groups (95% CI)	p-value
PR	30	43.8 (22.6)	35.4	52.3	-.89(-14.1, 12.4),	.894
MR	32	44.6 (29.0)	34.3	55.1		

Confidence interval (CI), manual restraint (MR), prolonged restraint (PR), p-values using independent t-tests

4.2.3.2. Quality of Upper Extremity Skills Test (QUEST)

Sixty-two participants completed the baseline QUEST assessment. It consists of four domains (dissociated movement, grasp, weight bearing and protective extension) which are scored separately and a total score computed. The assessments were complete at baseline other than seven protective extension domains which were not tested. Total and domain scores were compared across groups using independent t-

tests. There was a non-statistically significant difference between groups at baseline on the total scores -.67 (95% CI: -6.0, 7.3, p = .843), dissociated movement .62 (95% CI: -.55, 6.7, p = .841), grasp -5.61 (95% CI: -13.6, 2.4, p = .167), weight bearing -4.5 (95% CI: -10.3, 9.4, p = .928) and protective extension 5.26 (95% CI: -4.0, 14.6, p = .261). Table 4.11 outlines the baseline means and the difference across groups.

Table 4.8. Mean difference across groups of QUEST total and domain scores at baseline

	n	Baseline Mean (SD)	95% CI Lower	95% CI Upper	Difference in mean across groups (95% CI)	p-value
total scores						
PR	30	70.8(15.0)	65.3	76.4	-.67 (-7.3, 6.0)	.843
MR	32	71.5(11.1)	67.5	75.5		
dissociated movement						
PR	30	75.2(11.5)	70.9	79.5	.62 (-.55, 6.7)	.841
MR	32	74.6(12.5)	70.1	79.1		
grasp						
PR	30	60.3(13.9)	55	65.5	-5.61 (-13.6, 2.4)	.167
MR	32	65.9(17.4)	59.6	72.1		
weight bearing						
PR	30	74.0(24.7)	65	83.3	-4.5 (-10.3, 9.4)	.928
MR	32	74.5(2.5)	70	79.0		
protective extension						
PR	25	76.7(18.7)	69.0	84.4	5.26 (-4.0, 14.6)	.261
MR	30	71.5(15.7)	65.6	77.3		

Confidence interval (CI), manual restraint (MR), prolonged restraint (PR), p-values using independent t-tests

4.2.3.3. PedsQL4.0 Generic Core Scale

Parents/guardians of 51 participants were eligible to complete the PedsQL 4.0 Generic Core Scale as their child was two years or more. This scale consists of four dimensions (physical, emotional, social and nursery functioning). In addition, two summary scores were computed (i.e., psychosocial summary (emotional, social and nursery functioning dimensions) and total summary). A comparison of the scores across groups was made at baseline using independent t-tests. Two PedsQL 4.0 Generic Core Scales were not returned which reduced the number of cases to 49. In addition, there were 13 cases of the nursery functioning dimension excluded as they were less than 50% complete. Therefore, 36 cases for the nursery functioning dimension, the psychosocial summary and the total summary were compared. There was no statistically significant difference of the total summary score -.17 (95% CI:-7.9, 8.9, p = .966), the psychosocial summary score -1.13 (95% CI:-9.1, 6.9, p = .776) or the individual dimension scores across groups at baseline. Table 4.9. displays the baseline means of the summary and dimension scores and the difference in means across groups.

Table 4.9. Mean difference across groups of summary and dimension scores of the PedsQL 4.0 Generic Core Scale at baseline

	n	Baseline mean (SD)	95% CI Lower	95% CI Upper	Difference in mean across groups (95% CI)	p-value
summary						
PR	19	68.4 (12.2)	62.5	74.3	-.17 (-8.9, 7.9)	.966
MR	17	68.6 (11.6)	62.6	74.6		
psychosocial summary						
PR	19	73.3 (11.9)	67.6	79.0	-1.13 (-9.1, 6.9)	.776
MR	17	74.4 (11.5)	68.5	80.4		
physical functioning						
PR	25	53.6(20.3)	43.4	63.8	3.26(-8.1, 14.6)	.566
MR	24	49.9(19.1)	40.7	61.2		
emotional functioning						
PR	25	65.8 (20.0)	56.2	75.4	-1.56 (-12.1, 9.0)	.768
MR	24	68.2 (16.4)	59.7	76.7		
social functioning						
PR	25	87.4.8(12.7)	80.0	93.6	3.65 (-3.2, 10.5)	.289
MR	24	83.7 (11.0)	77.5	89.5		
nursery functioning						
PR	19	67.3(17.8)	58.7	75.9	-4.2 (-15.9, 7.4,)	.464
MR	17	71.6(16.4)	63.1	80.o		

Confidence interval (CI), manual restraint (MR), prolonged restraint (PR), p-values using independent t-tests

4.2.3.4. PedsQL 3.0 Cerebral Palsy (CP) Module

Fifty-one children were eligible to be assessed by their parents/guardians using the PedsQL 3.0 CP Module (in conjunction with the PedsQL 4.0 Generic Core Scale). The module consists of five dimensions (daily activities, movement and balance, pain and hurt, fatigue and eating activities). There were no summary scores computed for the module. Two modules were not returned at baseline therefore, 49 cases were

analysed. Table 4.10 illustrates the mean scores of the dimensions at baseline and the difference in mean scores across groups. There was not a statistically significant difference in any dimension between groups except, the daily activity dimension -12.08 (95% CI: -.160, - 23.9, p = .047) which demonstrated that children in the prolonged restraint group had more problems with activities of daily living (e.g., getting dressed and using the toilet).

Table 4.10. Mean difference across groups of dimension scores of the PedsQL 3.0 CP Module at baseline

Group	n	Baseline Mean(SD)	95% CI Lower	95% CI Upper	Difference in mean across groups (95% CI)	p-value
daily activities						
PR	25	14.8(16.3)	8.0	21.5	-12.08 (-.160, -23.9)	.047
MR	24	26.9 (24.5)	16.5	37.2		
movement and balance						
PR	25	55.6(23.7)	45.8	65.4	-6.06 (-20.2, 8.1)	.393
MR	24	61.7(25.6)	50.9	72.5		
pain and hurt						
PR	25	82.5(16.8)	75.6	89.4	7.5 (-4.8, 19.8)	.227
MR	24	75(25.4)	64.8	85.7		
fatigue						
PR	25	77(18.8))	69.2	84.8	1.22 (-9.5, 11.9)	.820
MR	24	75.8(18.5)	68.0	83.6		
eating activities						
PR	25	73.3(22.6)	64.0	82.6	-.18 (-12.6, 12.2)	.976
MR	24	73.4(20.5)	64.8	82.1		

Confidence interval (CI), manual restraint (MR), prolonged restraint (PR), p-values using independent t-tests

4.2.3.5. PedsQL Infant Scale

Eleven (11/62) participants in the trial were aged less than two years at baseline therefore, the parents/guardians of these children completed the PedsQL Infant Scale. This assessment consists of five dimensions (physical functioning, physical symptoms, emotional, social and cognitive functioning). In addition, a psychosocial health summary score (emotional, social and cognitive functioning dimension), a physical health summary score (physical functioning and physical symptom dimensions) and total score (all dimensions) were computed. There was no missing data from the PedsQL Infant Scale at baseline. The mean difference across groups of the total score -2.01 (95% CI: -20.4, 16.4, p = .810), the psychosocial summary -5.63 (95% CI: -26.6, 15.4, p = .560 or the physical summary 3.24 (95% CI: -16.3, 22.8, p = .716) was not statistically significantly different. The baseline means of the summary and dimension scores and the difference across groups are shown in Table 4.11.

Table 4.11. Mean difference across groups of summary and dimension scores of the PedsQL Infant Scale at baseline

	n	Baseline mean (SD)	95% CI Lower	95% CI Upper	Difference in mean across groups (95% CI)	p-value
Summary						
PR	4	83.1(12.6)	63.1	103.1	-2.01 (-20.4, 16.4)	.810
MR	7	85.1(13.1)	73.0	97.3		
Psychosocial summary						
PR	4	79.5(18.4)	50.3	108.7	-5.63 (-26.6, 15.4)	.560
MR	7	85.2(12.7)	73.4	96.9		
Physical summary						
PR	4	83.9(4.8)	76.1	91.5	3.24 (-16.3, 22.8)	.716
MR	7	80.6(16.5)	65.3	95.9		
Physical functioning						
PR	4	78.5(9.2)	63.9	93.0	1.09 (-24.1, 26.3,)	.924
MR	7	77.4(21)	58.1	96.6		
Physical symptoms						
PR	4	98.6(11.6)	80.0	117.2	5.75 (-19.7, 31.2)	.622
MR	7	92.9(20.4)	74.0	111.8		
Emotional functioning						
PR	4	72.9(24.9)	33.;3	112.5	-11.1(-34.3, 12.0)	.305
MR	7	84(9.6)	75.2	93.0		
Social functioning						
PR	4	93.8(7.5)	81.8	105.7	-2.6 (-15.2, 9.9)	.641
MR	7	96.4(9.4)	87.7	105.2		
Cognitive functioning						
PR	4	71.9(25.6)	31.2	112.6	3.08 (-32.6, 38.8)	.850
MR	7	75(25.0)	51.9	98.1		

Confidence interval (CI), manual restraint (MR), prolonged restraint (PR), p-values using independent t-tests

4.2.3.6. Birmingham Bimanual Questionnaire (BBMQ)

Of a possible 62 participants, eight did not complete the BBMQ at baseline and a further four completed version one which was excluded. Fifty participants were included in the comparison of the BBMQ across groups at baseline. There was no statistically significant difference -5.15 (95% CI: -16.5, 6.2, p = .364) demonstrated across groups. Table 4.12 shows the baseline means and the difference across groups.

Table 4.12. Mean difference across groups of the BBMQ scores at baseline

	n	Baseline means (SD)	95% CI Lower	95% CI Upper	Difference in mean across groups (95% CI)	p-value
PR	23	73.8 (16.1)	65.5	82.3	-5.15 (-6.2, 16.5)	.364
MR	27	68.6 (22.6)	59.5	77.25		

Confidence interval (CI), manual restraint (MR), prolonged restraint (PR), p-values using independent t-tests

4.3. Outcomes at ten-weeks

4.3.1. Primary outcome measure: Assisting Hand Assessment (AHA)

The primary outcome measure of the CATCH trial was the change in the AHA from baseline to the ten-week assessment. Sixty participants were included in the analysis. A total score is calculated (0-100 units) for this assessment tool with a higher score representing better bimanual skill. In the prolonged restraint group the mean change at the ten-week assessment was 9.0 (95% CI: 5.7, 12.3) logit-based 0-

100 AHA-units and in the manual restraint group 5.3 (95% CI: 1.3, 9.3) units. The difference in the change in mean scores was calculated using an independent t-test from baseline to ten-week assessment and found to be 3.68 (95% CI:-1.5, 8.8, p = .156) units and not statistically significant. Table 4.13 displays the baseline means and the difference in mean change across groups from baseline to the ten-week assessment.

A within group analysis was carried out using a paired t-test. The mean improvement at the ten-week assessment in the prolonged restraint group was 9.0 (95% CI: 5.65, 12.34, p = .000) units and 5.32 (95% CI: 1.34, 9.29, p = .010) units in the manual restraint group. The difference from baseline to ten-week assessment was statistically significant in both groups. Furthermore, Pearson's correlation coefficient (r) was computed to measure the size of the within group difference from baseline to ten-week assessment and found to be large (i.e., r = 0.5) in the prolonged restraint group and small (r = 0.2) in the manual restraint group. Table 4.14 shows the within group mean change on the AHA from baseline to ten-week assessment

.

Table 4.13. Baseline means of the AHA and the difference in mean change scores across groups from baseline to the ten-week assessment

	Mean(SD) baseline	95% CI Lower	95% CI Upper	n	Mean(SD) ten-week assessment	Mean (SD) change	95% CI Lower	95% CI Upper	Difference in mean change (95% CI)	p-value
PR	43.8 (22.6)	35.4	52.3	29	51.7(23.5)	9.0 (8.8)	5.7	12.3	3.68 (-1.5, 8.8)	.156
MR	44.6 (29.0)	34.3	55.1	31	49.7(30.0)	5.3 (10.8)	1.3	9.3		

Confidence interval (CI), manual restraint (MR) prolonged restraint (PR), p-values using independent t-tests

Table 4.14. Within group mean change on the AHA from baseline to ten-week assessment

AHA	n	Mean change	SD	95% CI Lower	95% CI Upper	t	df	p value	Effect size (r)
PR	29	9.00	8.8	5.65	12.35	5.5	28	.000	0.5
MR	31	5.32	10.8	1.34	9.29	2.7	30	.010	0.2

Confidence interval (CI), manual restraint (MR), prolonged restraint (PR), degrees of freedom (df), Pearson's correlation coefficient (r), p-values using dependent t-tests

The distribution of the mean change in AHA units at the ten-week assessment of individual cases across groups were displayed on a box and whisker diagram to examine the centre, spread overall range and possible outliers (see Figure 4.5). The interquartile ranges suggested the change in scores across groups was similar but larger in the prolonged restraint group. There were six outliers in total (four in the manual and two in the prolonged restraint group) with one case that demonstrated an extreme improvement in the manual restraint group. This case was identified and characteristics of the participant and the baseline and ten-week AHA assessments were re-examined. To examine the impact on the results a re-analysis was conducted with this case removed. The difference in the change in mean scores between the groups changed from 3.68 (95% CI:-1.15, 8.8, p = .156) units to 4.67 (95% CI:-.112, 9.44, p = .055) units.

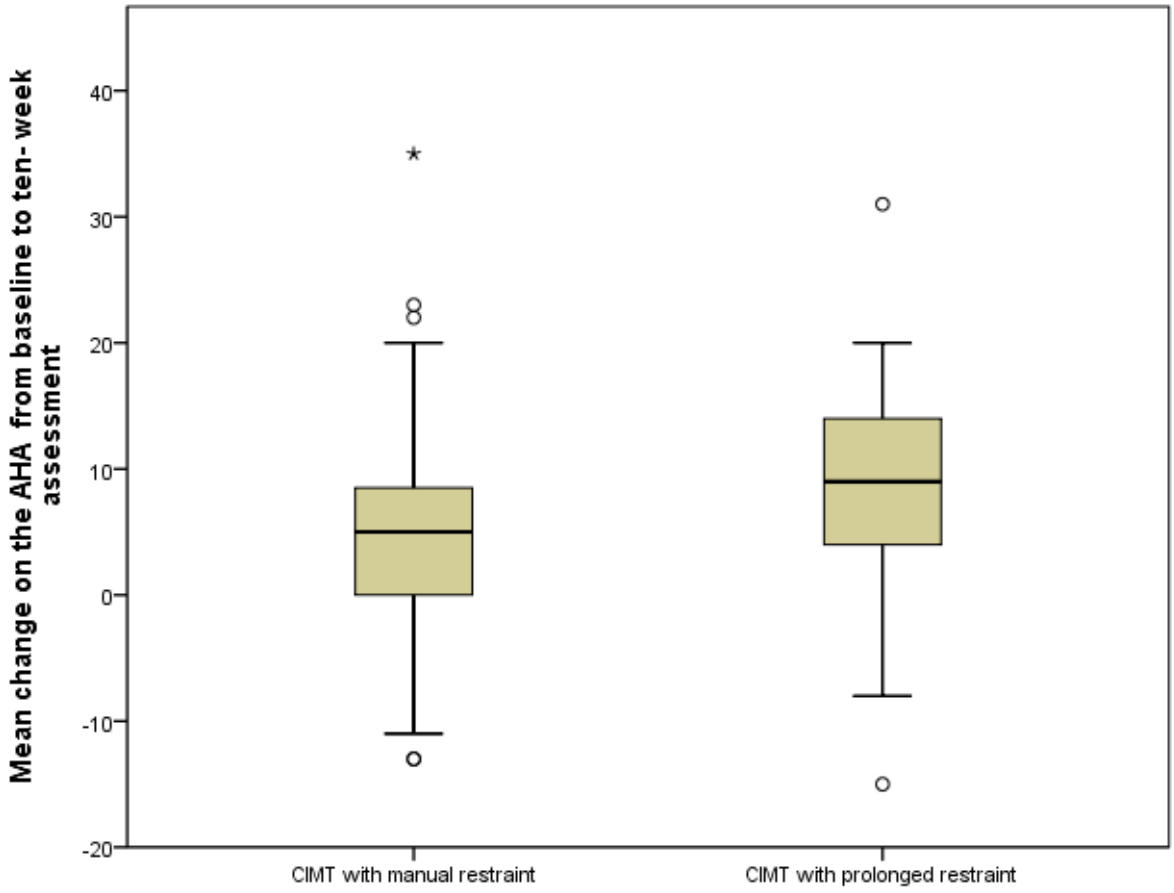


Figure 4.5. Distribution of the mean change across groups on the AHA from baseline to ten-week assessment

4.3.1.1. Exploratory regression analysis

In order to explore the impact of other independent variables as well as group allocation on the outcome, a regression analysis was conducted. This analysis measured the effect of different factors on the primary outcome (i.e. the logit-based 0-100 AHA-unit scale) at the ten-week assessment. The independent variables that may affect the score were identified based on theoretical and clinical reasoning. They included: group allocation; participant age; baseline clinical presentation (measured with QUEST and the AHA), amount of therapy delivered and compliance to the restraint of the delivered intervention. Table 4.15 lists the regression models and the strength of the effect of each on the AHA at ten-week assessment.

Table 4.15. Summary and strength of the effect of the regression models on the outcome on the AHA at ten-week assessment

Independent variable	Regression coefficient	R^2	F test model	p-value
Prolonged/manual restraint group	3.680	.034	2.060	.156
Age (months)	-.084	.007	.381	.539
Logit-based AHA unit scale at baseline	-.034	.008	.458	.501
Standardised summary QUEST score at baseline	.010	.000	.010	.921
Mean amount of therapy	.754	.004	.201	.656
Mean compliance to restraint	.840	.094	.455	.503

4.3.2. Quality of Upper Extremity Skills Test (QUEST)

The QUEST consists of a total and individual domain scores which are calculated as percentages with a higher percentage representing better skill. The mean change scores from baseline to ten-week assessment on QUEST were compared using independent t-tests across groups. Sixty participants were included in the comparison. A number of domains were not tested and therefore, excluded. Seven protective extension domains at baseline and four at the ten-week assessment (three cases were missing at both time points) therefore, eight cases had the domain excluded from the analysis. One weight bearing domain was not tested at the ten-week assessment, therefore 59 cases with this domain were included. Baseline means and difference in mean change across groups from baseline to the ten-week assessment are shown in Table 4.16.

The prolonged and manual restraint groups both demonstrated a small deterioration at the ten-week assessment in total QUEST mean scores -1.5 (95% CI: -4.9, 1.9 and -1.6 (95% CI:-4.5, 1.3) respectively, with a group difference of .08 (95% CI:-4.6, 4.5, p = .970). Dissociated movement improved in both groups but more in the manual restraint group with a difference across groups of -.63 (95% CI:-5.2, 4.0, p = 784). Grasp and weight bearing improved in the prolonged restraint group but not in the manual restraint group and the group difference was 3.3 (95% CI:-2.1, 8.7, p = .227) and 2.2 (95% CI:-5.2, 9.7, p = .551) respectively. Protective extension was found to deteriorate in both groups but less so in the prolonged restraint group. The group difference was 1.6 (95% CI:-9.0, 12.2, p = .758). The differences in mean change

across groups from baseline to ten-week assessment were not statistically significant.

Table 4.16. Mean difference across groups of QUEST total and domain scores between baseline and ten-week assessment

	Baseline Mean (SD)	95% CI Lower	95% CI Upper	n	ten-weeks Mean(SD)	Mean(SD) change	95% CI Lower	95% CI Upper	Difference in mean change (95% CI)	p-value
total scores										
PR	70.8 (15.0)	65.3	76.4	29	71.6 (11.7)	-1.5 (8.9)	-4.9	1.9	.08 (95% CI-4.6,4.5)	.970
MR	71.5 (11.1)	67.5	75.5	31	73.3(11.7)	-1.6 (7.8)	-4.5	1.3		
dissociated movement										
PR	75.2 (11.5)	70.9	79.5	29	76.0 (9.7)	1.6 (8.3)	-1.5	4.75	-.63 (95% CI-5.2,4.0)	.784
MR	74.6 (12.5)	70.1	79.1	31	77.0 (10.3)	2.2 (9.5)	-1.2	5.7		
grasp										
PR	60.3 (13.9)	55	65.5	29	62.0 (14.7)	2.9 (10.3)	-1.1	6.8	3.3 (95% CI-2.1, 8.7)	.227
MR	65.9 (17.4)	59.6	72.1	31	65.3 (17.6)	-0.5 (10.7)	-4.4	3.5		
weight bearing										
PR	74.0 (24.7)	65	83.3	28	78.2 (13.7)	2.1 (18.3)	-4.5	9.2	2.2 (95% CI-5.2, 9.7)	.551
MR	74.5 (2.5)	70	79	31	74.4 (13.5)	-0.1 (9.15)	-3.5	3.2		
protective extension										
PR	76.7 (18.7)	69.0	84.4	24	73.4 (16.8)	-.43	-9.8	5.64	1.6 (95% CI: -9.0, 12.2)	.758
MR	71.5 (15.7)	65.6	77.3	28	70.5 (15.2)	-2.0 (19.9)	-8.0	7.1		

Confidence interval (CI), manual restraint (MR), prolonged restraint (PR).degrees of freedom (df), p-values using independent t-tests

A within group comparison using a paired t-test of the mean change of QUEST from baseline to the ten-week assessment was conducted. The mean improvement at the ten-week assessment in QUEST total scores in the prolonged restraint group was 1.50 (95% CI:-1.9, 4.9) and 1.58 (95% CI:-1.35, 4.51) in the manual restraint group and not statistically significantly different ($p = .37$). Similarly, the mean change scores of the QUEST domains were compared within groups across baseline and ten-week time points and none found to be statistically significantly different. The within group difference of QUEST total and domain scores from baseline to ten-week assessment are outlined in Table 4.17.

Table 4.17. Within group difference of QUEST total and domain scores from baseline to ten-week assessment

	n	Mean change	SD	95% CI Lower	95% CI Upper	t	df	p-value
total								
PR	29	1.50	8.95	-1.90	4.90	.903	28	.37
MR	31	1.58	7.99	-1.35	4.51	1.10	30	.278
dissociated movement								
PR	29	1.60	8.27	-1.54	4.75	1.04	28	.304
MR	31	2.23	9.47	-1.23	5.71	1.3	30	.198
grasp								
PR	29	2.87	10.34	-1.06	6.8	1.49	28	.146
MR	31	-.448	10.71	-4.38	3.48	-.233	30	.817
weight bearing								
PR	28	2.11	18.34	-4.99	9.22	.610	27	.574
MR	31	-.115	9.16	-3.47	3.24	-.07	30	.945
protective extension								
PR	24	-.433	17.82	-7.96	7.09	-.119	23	.906
MR	28	-2.06	19.86	-9.76	5.63	-.55	27	.587

Confidence interval (CI), manual restraint (MR), prolonged restraint (PR).degrees of freedom (df), p-values using dependent t-test

4.3.3. PedsQL 4.0 Generic Core Scales

An analysis of the difference in mean change scores across groups between baseline and ten-week assessment was made using independent t-tests. Two questionnaires were not returned at baseline and a further two at the ten-week assessment which reduced the number to 47 cases. In addition, there were two cases where the PedsQL Infant Scale at the ten-week was administered in error therefore, 45 cases were included in the comparison. There were 13 cases where the

nursery dimension was missing (i.e., less than 50 % complete) consequently, 32 cases of this dimension (and summaries with the dimension) were included.

There was an improvement in both groups in the total, physical summary and emotional functioning scores. It was greater in the prolonged restraint group in the total score 2.73 (95% CI:-7.09, 12, 6, p = .574) but less in this group for physical summary -5.14 (95% CI:-16.4, 6.1, p = .361) and emotional functioning -3.44 (95% CI:-14.4, 7.5, p = .531). There was improvement in the psychosocial summary scores and in nursery functioning in the prolonged restraint group but decline in the manual restraint group with a difference of 4.79 (95% CI:-7.4, 16.9, 7.4, p = 428) and 14.33 (95% CI:-1.4, 30.1, p = .073), respectively. Social functioning deteriorated in both groups but more in the prolonged restraint group -4.47 (95% CI:-17.8, 8.8, p = .500).The findings of the analyses were not statistically significant. Baseline means and the differences in mean change across groups are outlined in Table 4.18.

Table 4.18. Mean difference across groups of the change in summary and dimension scores of the PedsQL 4.0 Generic Core Scale from baseline to ten week assessment.

	Baseline mean (SD)	95% CI Lower	95% CI Upper	n	Mean (SD) change	95% CI Lower	95% CI Upper	Difference in mean change (95% CI)	p-value
total									
PR	68.4 (12.2)	62.5	74.3	15	3.9 (11.3)	-2.3	10.2	2.73 (-7.09, 12.6)	.574
MR	68.6 (11.6)	62.6	74.6	17	1.2 (15.3)	-6.6	9.0		
psychosocial summary									
PR	73.3(11.9)	67.6	79.0	15	2.9 (14.2)	-5.0	10.7	4.79 (-7.4, 16.9)	.428
MR	74.4 (11.5)	68.5	80.4	17	-1.9 (18)	-11.6	7.7		
physical summary									
PR	53.6 (20.3)	43.4	63.8	22	4.4 (14.6)	-2	10.9	-5.14 (-16.4, 6.1)	.361
MR	49.9 (19.1)	40.7	61.2	23	9.5 (21.9)	.04	19.0		
emotional functioning									
PR	65.8(20.0)	56.2	75.4	22	1.9 18.7)	-6.3	10.3	-3.44 (-14.4, 7.5)	.531
MR	68.2(16.4)	59.7	76.7	23	5.4 (17.8)	-2.3	13.1		
social functioning									
PR	86.8(12.7)	80.0	93.6	22	-10.5 (18)	-18.0	-2.5	-4.47 (-17.8, 8.8)	.500
MR	83.5 (11.0)	77.5	89.5	23	-6.0 (25.4)	-17.0	5.0		
nursery functioning									
PR	67.3 (17.8)	58.7	75.9	15	11.3 (19)	0.8	22.0	14.33 (-1.4, 30.1)	.073
MR	71.6 (16.4)	63.1	80.o	17	-2.9 (24)	-15.2	9.4		

Manual restraint (MR), prolonged restraint (PR), p-values using independent t-tests

4.3.4. PedsQL 3.0 Cerebral Palsy (CP) Module

A group comparison of the difference in mean change between baseline and ten-week of the PedsQL 3.0 CP Module was made using independent t-tests. The module consists of five dimensions (daily activities, movement and balance, pain and hurt, fatigue and eating activities). Each dimension is scored on a scale of 0-100 and a higher score represents better HRQOL. Fifty-one participants were eligible to be assessed with the module however, two modules were not returned at baseline or the ten-week assessment. Of the remaining 47 cases, there were two where the PedsQL infant scale was administered in error at the ten-week assessment .Therefore, 45 cases were included in the analyses. A number of returned modules had dimensions which were excluded (less than 50% complete). This included; two cases of daily activity, one case of movement and balance, two cases of pain and hurt and one case of the fatigue dimension, all at the ten-week assessment.

There was improvement in both groups on daily activity pain and hurt and eating activity which was greater in the prolonged restraint group for daily activity 1.16 (95% CI:-14.8, 17.1, p = .883) but there was less improvement in pain and hurt -5.35 (95% CI:-16.0, 5.3, p = .318), and eating activity -2.87 (95% CI:-15.20, 9.5, p = .642). Movement and balance was better in the prolonged restraint group but declined in the manual restraint group with a difference of 10.05 (95% CI:-5.3, 25.4, p = .193). Fatigue deteriorated in both groups but to a greater extent in the prolonged restraint group with a group difference of -7.54 (95% CI: - 21.7, 6.6, p = .287). Baseline means

and difference in mean change across groups from baseline to ten-week assessment are shown in Table 4.19. There were no statistically significant findings.

Table 4.19. Mean difference across groups of dimension scores of the PedsQL 3.0 CP Module from baseline to ten-week assessment.

Group	Baseline Mean(SD)	95% CI Lower	95% CI Upper	n	Mean (SD) change	95% CI Lower	95% CI Upper	Difference in mean change (95% CI)	p-value
daily activity									
PR	14.8(16.3)	8.0	21.5	20	9.8 (22.8)	-0.9	20.4	1.16 (-14.8, 17.1)	.883
MR	26.9 (24.5)	16.5	37.2	23	8.6 (28.0)	-3.6	20.7		
movement and balance									
PR	55.6(23.7)	45.8	65.4	22	8.0 (23.0)	-2.3	18.3	10.05 (-5.3, 25.4)	.193
MR	61.7(25.6)	50.9	72.5	22	-2.1(27.0)	-14.1	9.9		
pain and hurt									
PR	82.5(16.8)	75.6	89.4	20	0.6 (19.2)	-8.4	9.6	-5.35 (-16.0, 5.3)	.318
MR	75(25.4)	64.8	85.7	23	6.0 (15.5)	-.7.0	12.6		
fatigue									
PR	77(18.8))	69.2	84.8	21	-8.6 (25.4)	-20.2	2.9	-7.54 (-21.7, 6.6)	.287
MR	75.8(18.5)	68.0	83.6	23	-1.0 (20.9)	-10.1	8.0		
eating activities									
PR	73.3(22.6)	64.0	82.6	22	2.8 (20.7)	-6.0	12.0	-2.87 (-15.20, 9.5)	.642
MR	73.4(20.5)	64.8	82.1	23	5.7 (20.3)	-3.0	14.5		

Manual restraint (MR), prolonged restraint (PR), p-values using independent t-tests

4.3.5. PedsQL Infant Scale

An analysis across groups of the change in the PedsQL Infant Scale from baseline to ten-week assessment was conducted using independent t-tests. This assessment consists of five dimensions (physical functioning, physical symptoms, emotional, social and cognitive functioning) and a psychosocial health summary, a physical health summary and total score. Each dimension and summary is scored on a scale of 0-100 and a higher score represents better HRQOL. The 11 cases that completed the PedsQL Infant Scale were included.

A decline in the manual restraint group with improvement in the prolonged restraint group was noted in the summary, psychosocial summary, physical functioning and cognitive functioning. The difference in mean change score across groups respectively was; 11.6 (95% CI: -26.4, 3.2, p = .145), 11.56 (95% CI: -30.2, 7.0, p = .193), 8.51 (95% CI: -20.9, 3.9, p = .155) and 12.16 (95% CI: -36.9, 12.6, p = .295). In addition, physical symptoms and emotional functioning deteriorated in both groups with more deterioration in the manual restraint group. In the former there was a difference across groups of 4.51 (95% CI:-16.2, 7.1, p = .404) and the latter, 10.01 (95% CI: -33.0, 12.3, p = .329). However, in the social functioning dimension there was improvement in the manual restraint group and deterioration in the manual restraint group with a difference of -2.32 (95% CI: -18.0, 13.4, p = .746). The differences in mean change scores across groups were not statistically significant. The baseline means and differences in mean change from baseline to ten weeks are shown in Table 4.20.

Table 4.20. Mean difference of the PedsQL Infant Scale from baseline to ten-week assessment.

	Baseline mean (SD)	95% CI Lower	95% CI Upper	n	Mean(SD) change	95% CI Lower	95% CI Upper	Difference in mean change (95% CI)	p-value
summary									
PR	83.1(12.6)	63.1	103.1	4	0.17(42.0)	-6.6	6.9	11.6 (-26.4, 3.2)	.145
MR	85.1(13.1)	73.0	97.3	7	-10 .0 (12.0)	-21.4	1.2		
psychosocial summary									
PR	79.5(18.4)	50.3	108.7	4	1.1 (3.8)	-5.0	7.2	11.56 (-30.2, 7.0)	.193
MR	85.2(12.7)	73.4	96.9	7	-10.5 (16.0)	-25.1	4.1		
physical summary									
PR	83.9(4.8)	76.1	91.5	4	3.4(8.2)	-9.7	16.6	8.51 (-20.9, 3.9)	.155
MR	80.6(16.5)	65.3	95.9	7	-5.0(9.0)	-13.41	3.2		
physical functioning									
PR	78.5(9.2)	63.9	93.0	4	3.05(16.2)	-22.7	28.8	12.16 (-36.9, 12.6)	.295
MR	77.4(21)	58.1	96.6	7	-9.1(18.0)	-25.7	7.6		
physical symptoms									
PR	98.6(11.6)	80.0	117.2	4	-5.5(11.4)	-23.7	12.7	4.51 (-7.1, 16.2)	.404
MR	92.9(20.4)	74.0	111.8	7	-10.0 (6.0)	-15.6	-4.4		
emotional functioning									
PR	72.9(24.9)	33.;3	112.5	4	-1.9 (7.8)	-14.4	10.45	10.01 (-33.0, 12.3)	.329
MR	84(9.6)	75.2	93.0	7	-12.3 (18.8)	-29.7	5.0		
social functioning									
PR	93.8(7.5)	81.8	105.7	4	-1.3(6.3)	-11.26	8.8	-2.32 (-18.0, 13.4)	.746
MR	96.4(9.4)	87.7	105.2	7	3.6(12.8)	-15.4	8.3		
cognitive functioning									
PR	71.9(25.6)	31.2	112.6	4	6.5 (7.9)	-6.0	19.1	22.02 (-44.5, .5)	.054
MR	75(25.0)	51.9	98.1	7	-15.5 (18.6)	-32.7	1.7		

Manual restraint (MR), prolonged restraint (PR), p-values using independent t-tests

4.3.6. Birmingham Bimanual Questionnaire (BBMQ)

A comparison was conducted across groups of the change scores from baseline to ten-week assessment in the BBMQ using an independent t-test. A total percentage score was calculated for the BBMQ with a higher score representing better bimanual skill. Fifty questionnaires were completed at the baseline assessment. There were two cases of non-returned BBMQs at the ten-week assessment but these cases had a missing BBMQ at baseline consequently, change scores from baseline to ten-week assessment included 50 cases.

The difference in the mean change in the children at ten weeks across groups was 16.9 (95% CI: 2.9, 30.9, p = .019) and statistically significantly greater in the prolonged restraint group. Table 4.21 illustrates the baseline means and the difference in mean change across groups from baseline to the ten-week assessment.

Table 4.21. Mean difference across groups of the BBMQ scores at baseline and ten-week assessment

	Baseline means (SD)	95% CI Lower	95% CI Upper	n	Mean (SD) change assessment	Difference in mean change (95% CI)	p-value
PR	73.8 (16.1)	65.5	82.3	23	20.9 (25.9)	16.91 (2.9, 30.9)	.019*
MR	68.6 (22.6)	59.5	77.25	27	4.0 (23.4)		

*Statistically significant (p<.05), manual restraint (MR), prolonged restraint (PR), p-values using independent t-tests

4.4. Outcomes at 24-weeks

4.4.1.PedsQL 4.0 Generic Core Scale

A comparison of the change in scores across groups of the PedsQL 4.0 Generic Core Scale between baseline and 24-weeks was made using independent t-tests. Of the 51 scales completed, six questionnaires were not returned at either baseline or 24-weeks. Therefore, 45 cases were included in the analysis. Thirteen cases had a nursery functioning dimension missing. Therefore, the nursery dimension, psychosocial and summary comparisons had 32 cases included. Except for the physical functioning dimension there was deterioration in the means from baseline to the 24 week assessment for the analyses conducted. The deterioration was greater in the prolonged restraint group for the summary -1.72 (95% CI:-12.8, 9.3, p = .754), psychosocial summary, -1.90 (95% CI:-14.4, 10.6, p = .758), physical functioning -.35 (95% CI:-12.2, 11.6, p = .954), social functioning -1.58 (95% CI:-15.4, 2.3, p = .818) and nursery functioning-7.03 (95% CI:-23.4, .3, 4, p = .386). However, emotional functioning was reported to show improvement in both groups but more so in the prolonged restraint group 1.69 (95% CI:-8.6, 12.0, p = .742). None of the findings were statistically significant. The changes in mean scores and the differences across groups are shown in Table 4.22.

The ten-week and 24-week scores of the PedsQL 4.0 Generic Core Scale across groups were analysed. There were six cases not returned at either the ten-week or the 24-week assessment or both time points. In addition, there were two mismatched

questionnaires between the ten-week and 24 week assessments and the PedsQL Infant Scale was used instead. Therefore, 43 cases were included in this analysis. Deterioration in mean scores was demonstrated in both groups from ten-week to 24-week assessments in every score (except nursery functioning for the manual restraint group)

The deterioration was greater in the prolonged restraint group for the summary -4.48 (95% CI: -15.2, 6.2, p = .400), psychosocial summary -5.15 (95% CI: -16.8, 6.5, p = .372), and nursery functioning -14.37 (95% CI: -30.2, 1.5, p = .07, p = .074). Whereas there was less decline in the prolonged restraint group for physical functioning 3.02 (95% CI: -9.3, 15.3, p = .622), emotional functioning 6.20 (95% CI: -5.4, 17.8, p = .286) and social function 1.52 (95% CI: -9.1, 12.1, p = .744). None of the findings were statistically significant and the mean changes and differences across groups are shown in Table 4.22.

Table 4.22. Mean difference across groups of the dimension and summary scores of the PedsQL 4.0 Generic Core Scale between baseline and 24-week assessment and ten-week and 24-week assessment.

Baseline and 24–week assessment							Ten and 24-week assessment					
	n	Mean (SD) change	95% CI Lower	95% CI Upper	Diff in mean change (95% CI)	p-value	n	Mean (SD) change	95% CI Lower	95% CI Upper	Diff in mean change (95% CI)	p-value
summary												
PR	16	-6.0 (17.3)	-15.5	3.0	-1.72 (-12.8, 9.3,)	.754	15	-11.2 (15.6)	-20.0	-2.5	-4.48(-15.2, 6.2,)	.400
MR	16	-4.5 (13.0)	-11.4	2.4			17	-6.7 (14.0)	-14.0	0.5		
psychosocial summary												
PR	16	-6.0 (19.1)	-17	3.3	-1.90(-14.4, 10.6,)	.758	15	-9.4 (16.3)	-18.4	-0.3	-5.15(-16.8, 6.5,)	.372
MR	16	-5.0 (15.0)	-13	3.0			17	-4.2 (15.7)	-12.3	3.9		
physical functioning												
PR	21	-6.5 (19.2)	-15.3	2.3	-.35 (-12.2, 11.6,)	.954	19	-13.4 (20.0)	-23.0	-3.7	3.02(-9.3, 15.3)	.622
MR	24	-6.2 (20.2)	-14.7	2.4			24	-16.3 (19.3)	-24.6	-8.1		
emotional functioning												
PR	21	1.9(20.6)	-7.5	11.3	1.69(-8.6, 12.0,)	.742	19	-0.46(20.0)	-10.1	9.2	6.20(-5.4, 17.8)	.286
MR	24	0.2(13.5)	-5.5	5.9			24	-6.7(17.5)	-14.0	0.7		
social functioning												
PR	21	-19.8 (24.5)	-31.0	-8.7	-1.58(-15.4, 2.3)	.818	19	-8.9 (15.3)	-16.3	-1.6	1.52(-9.1, 12.1)	.744
MR	24	-18.2(21.5)	-27.3	-9.0			24	-10.5(19.1)	-18.6	-2.4		
nursery functioning												
PR	16	-8.6 (24.0)	-21.4	4.1	-7.03 (-23.4, .3,4)	.386	15	-13.9 (23.0)	-27.0	-.87	-14.37(-30.2, 1.5)	.074
MR	16	-1.6(21.1)	-12.8	9.7			17	0.49(20.5)	-10.0	11.0		

Manual restraint (MR), prolonged restraint (PR), p-values using independent t-tests

4.4.2. PedsQL 3.0 Cerebral Palsy (CP) Module

Comparison between the baseline and 24-week change in mean scores of the PedsQL 3.0 CP Module across groups was made using independent t-tests. Of the 51 completed modules, six cases were not returned at either time point. Therefore, there were 45 cases in the analysis. All dimensions were completed. Both groups demonstrated a mean improvement in daily activity but more in the manual restraint group -2.15 (95% CI: -15.6, 1.3, p = .748). However, both groups deteriorated in movement and balance, pain and hurt and fatigue. The amount of deterioration was greater in the prolonged restraint group for pain and hurt -7.86 (95% CI: -21.6, 5.9, p = .225) but less for movement and balance 4.91 (95% CI: -8.8, 17.9, p = .449) and fatigue .79 (95% CI: -11.6, 13.2, p = .898). Furthermore, although eating activity were reported to deteriorate in the manual restraint group at the 24 week time point there was some improvement in the prolonged restraint group with a group difference of 7.27 (95% CI: -5.6, 20.2, p = 261). None of the group differences were statistically significant. Table 4.26 shows the mean changes between baseline and 24 week assessment and the group differences.

The change scores from the ten-week assessment to the 24-week assessment on the PedsQL 3.0 Cerebral Palsy Module were compared across groups using independent t-tests. Six cases had modules not returned at either the ten-week or the 24-week assessment. In addition, there were two inconsistencies and the PedsQL infant Scale was used instead. Forty three cases were included in the analysis. A number of the PedsQL 3.0 CP Module had missing dimensions at the ten-week

assessment. This included two movement and balance, two daily activities, two pain and hurt and one fatigue. Therefore the number of cases analysing these dimensions was reduced. Both groups demonstrated deterioration in mean scores from ten week to 24-week assessment across groups for all dimensions. This was greater in the prolonged restraint group for daily activity -2.02 (95% CI: -16.7, 12.7, p = .781), movement and balance-5.76 (95% CI: -20.9, 9.4, p = .448) and pain and hurt -2.42 (95% CI: -13.7, 8.9, p = .670). Although it was greater in the manual restraint group for fatigue 2.86 (95% CI: -11.1, 16.8, p = .691) and eating activity 8.19 (95% CI: -4.5, 20.9 p = .198). No statistically significant differences were found across groups. Mean changes and the differences across groups are outlined in Table 4.23.

Table 4.23. Mean difference across groups of the PedsQL 3.0 CP module between baseline and 24-week assessment and ten-week and 24-week assessment.

Baseline and 24–week assessment							Ten and 24-week assessment					
	n	Mean (SD) change	95% CI Lower	95% CI Upper	Difference in mean change (95% CI)	p-value	n	Mean (SD) change	95% CI Lower	95% CI Upper	Difference in mean change (95% CI)	p-value
daily activities												
PR	22	5.5(16.7)	-1.9	12.9	-2.15 (-15.6, 1.3)	.748	18	-2.5(23.0)	-14.0	9.0	-2.02 (-16.7, 12.7)	.781
MR	23	7.6(26.6)	-3.9	19.1			23	-0.5(23.1)	-10.5	9.5		
movement and balance												
PR	22	-2(20.6)	-11.1	7.0	4.91 (-8.8, 17.9)	.449	20	-10.3(23.5)	-21.2	0.7	-5.76 (-20.9, 9.4)	.448
MR	23	-6.9(22.3)	-16.6	2.7			22	-4.5(25.0)	-15.7	6.7		
pain and hurt												
PR	22	-5.7(23.9)	-16.3	4.9	-7.86 (-21.6, 5.9)	.225	18	-4.9(21.0)	-15.3	5.6	-2.42 (-13.7, 8.9)	.670
MR	23	2.2(21.9)	-7.2	11.6			23	-2.4(15.0)	-9.0	4.0		
fatigue												
PR	22	-6.8(19.7)	-15.5	1.9	.79 (-11.6, 13.2)	.898	19	-2.3(22.0)	-12.7	8.0	2.86 (-11.1, 16.8)	.691
MR	23	-7.6(21.6)	-16.9	1.7			23	-5.2(23.0)	-15.0	4.7		
eating activities												
PR	22	0.57(22.2)	-9.3	10.4	7.27 (-5.6, 20.2)	.261	20	-3.1(20.6)	-12.7	6.5	8.19 (-4.5, 20.9)	.198
MR	23	-6.7(20.6)	-15.6	2.2			23	-11.3(20.5)	-20.2	-2.5		

Manual restraint (MR), prolonged restraint (PR), p-values using independent t-tests

4.4.3. PedsQL Infant Scale

A comparison was made across groups of the differences in mean change scores from baseline to 24-week follow-up measured with the PedsQL Infant Scale using independent t-tests. Eleven assessments were completed however, only nine included as two cases had a PedsQL 4.0 Generic Score Scale administered in error at 24 week follow-up and therefore, were excluded. The psychosocial summary and emotional and cognitive functioning showed improvement in the prolonged restraint group but deterioration in the manual restraint group. Furthermore, the difference across groups was statistically significantly different in the psychosocial summary 9.73 (95% CI: 4.6, 14.9, p = .003) and the emotional functioning 15.66 (95% CI: 5.5, 25.9, p = .009) although, not for cognitive functioning, 15.01(95% CI: -2.4, 32.5, p = .081).

A number of mean scores (summary, physical summary, physical functioning) demonstrated a decline within both groups but less so in the prolonged restraint group. The difference across groups for these scores were; summary 6.94 (95% CI: 2.76, 11.1, p = .006; statistically significant different), physical summary 2.76 (-9.4, 15.3, p = .618), physical functioning 2.46 (95% CI:-30.2, 35.1, p = .864) and physical symptoms 3.07 (95% CI:-10.8, 16.9, p = .616). Although social functioning declined across groups it did so more in the prolonged restraint group.-1.50 (95% CI: -7.3, 4.3, p = .563). Table 4.27 outlines the mean change from baseline to 24 week follow–up and the difference in change across groups. The scores which demonstrated a statistically significant differences across groups were investigated further by

administration of a paired t-test to examine the within group change in scores from baseline to 24 weeks. In the manual restraint group there was a statistically significant decline from baseline to 24 week follow-up in the summary score -9.4 (95% CI: -13.4, -5.5, p = .003), psychosocial summary -8.2 (95% CI: -12.5, -3.9, p = .006) and in emotional functioning -13.1 (95% CI: -21.8, -4.4, p = .014), However, a similar decline not found in the prolonged restraint group the summary score -2.5 (95% CI: -5.0, 0.12, p = .056), psychosocial summary 1.5 (95% CI: -3.1, 6.2, p = .378) and in emotional functioning 2.6 (95% CI: -6.5, 11.6, p = .436).

The difference in mean change scores from ten-week assessment to 24-week follow-up were compared across groups. There were nine cases included in the analysis. Both groups demonstrated a mean improvement in psychosocial summary with less improvement in the prolonged restraint group -4.89 (95% CI: -22.9, 13.1, p = .541) and emotional functioning with more improvement in the prolonged restraint group 2.87 (95% CI: -19.9, 25.6, p = .774). For a number of scores (i.e., summary, physical summary, physical functioning and social functioning) there was deterioration in the prolonged restraint group with improvement in the manual restraint group. The differences across groups for the summary score was -6.23 (95% CI:-21.4, 8.9, p = .383), physical summary -8.25 (95% CI: -20.8, 4.3, p = .164), physical functioning -15.01(95% CI: -35.5, 5.4, p = .127) and social functioning -8.25 (95% CI:-23.5, 7.0, p = .242). Although, both groups deteriorated in physical symptoms it was to a greater extent in the prolonged restraint group -1.50 (95% CI: -15.0, 12.0, p = .800). No statistically significant differences were demonstrated across groups. Table 4.24

outlines the mean change from ten-week assessment to 24 week follow–up and the difference in change across groups.

Table 4.24. Mean differences across groups of the PedsQL Infant Scale between baseline and 24-week assessment and ten-week and 24-week assessment.

Baseline and 24–week assessment							Ten and 24-week assessment					
	n	Mean (SD) change baseline to 24-weeks	95% CI Lower	95% CI Upper	Difference in mean change (95% CI)	p-	n	Mean (SD) change ten to 24-weeks	95% CI Lower	95% CI Upper	Difference in mean change(95% CI)	p-
summary												
PR	4	-2.5 (1.6)	-5.0	0.12	6.94	.006*	4	-2.7 (3.7)	-8.6	3.3	-6.23	.383
MR	5	-9.4 (3.2)	-13.4	-5.5	(2.76, 11.1)		5	3.6 (12.2)	-11.6	18.8	(-21.4, 8.9,)	
psychosocial summary												
PR	4	1.5(2.9)	-3.1	6.2	9.73	.003*	4	0.4 (3.4)	-5.0	5.8	-4.89	.541
MR	5	-8.2(3.5)	-12.5	-3.9	(4.6, 14.9)		5	5.3 (14.7)	-13.0	23.6	(-22.9, 13.1)	
physical summary												
PR	4	-3.8(7.5)	-15.8	8.2	2.76	.618	4	-7.2(5.4)	-16.0	1.5	-8.25	.164
MR	5	-6.6(8.1)	-16.7	3.5	(-9.4, 15.3)		5	1.0(9.3)	-10.6	12.6	(-20.8, 4.3)	
physical functioning												
PR	4	-8.9(21.2)	-42.6	24.8	2.46	.864	4	-12.0 (6.0)	-21.4	-2.6	-15.01	.127
MR	5	-11.4(20.1)	-36.7	13.6	(-30.2, 35.1)		5	3.0 (16.3)	-17.2	23.3	(-35.5, 5.4)	
physical symptoms												
PR	4	-8(9.9)	-23.7	7.7	3.07	.616	4	-2.5 (10.6)	-19.4	14.4	-1.50	.800
MR	5	-11(7.7)	-20.7	-1.5	(-10.8, 16.9)		5	-1.0 (6.5)	-9.0	7.0	(-15.0, 12.0)	
emotional functioning												
PR	4	2.6(5.7)	-6.5	11.6	15.66	.009*	4	4.5 (9.7)	-10.9	28.5	2.87	.774
MR	5	-13.1(7.0)	-21.8	-4.4	(5.5, 25.9)		5	1.6 (17.0)	-19.5	22.8	(-19.9, 25.6)	
social functioning												
PR	4	-2.5(5.0)	-10.5	5.5	-1.50	.563	4	-1.3 (2.5)	-5.2	2.7	-8.25	.242
MR	5	-1.0(2.2)	-3.7	1.8	(-7.3, 4.3)		5	7.0(12.5)	-7.0	22.6	(-23.5, 7.0)	
cognitive functioning												
PR	4	4.6 (5.7)	4.6	13.6	15.01	.081	4	-2.0 (4.7)	-9.6	5.5	-9.30	.342
MR	5	-10.6(13.7)	-27.5	-3.9	(-2.4, 32.5)		5	7.2 (17.5)	-14.5	28.9	(-30.7, 12.1)	

Manual restraint (MR), prolonged restraint (PR), p-values using independent t-tests

4.4.4. Birmingham Bimanual Questionnaire (BBMQ)

The BBMQ was evaluated by comparison of change scores between the baseline and 24-week assessment using independent t-tests. Fifty BBMQs were completed at baseline however, three were not returned at the 24-week assessment (one had a baseline assessment missing). Therefore 48 cases were included in the analysis. Both groups demonstrated an improvement at 24 week assessment but it was greater in the prolonged restraint group with a difference across groups of 1.1 (95% CI: -12.5, 14.6, p = .873). Baseline means and change across time points are shown in Table 4.28. Comparison between the ten–week and 24-week mean change scores across groups was also made. Two BBMQs were not returned at the ten-week assessment (60/62) and three cases (59/62) at the 24-week assessment therefore, 59 cases were included in the analysis. Mean change of the BBMQ scores across groups revealed a statistically significant greater deterioration in the prolonged restraint group of-13.5 (95% CI: -24.9, -2.1, p = .021). The mean changes and differences across groups are outlined in Table 4.25.

Table 4.25. Mean difference across groups of the BBMQ from baseline and 24-week assessment and from ten-week and 24-week assessment.

Baseline and 24- week assessment						Ten and 24-week assessment			
	Baseline mean (SD)	n	Mean (SD) change	Diff in mean change (95% CI)	p-value	n	Mean (SD) change	Diff in mean change (95% CI)	p-value
PR	73.8 (16.1)	21	3.1 (25.1)	1.1 (-12.5, 14.6)	.873	27	-13.6 (23.2)	-13.5 (-24.9, -2.1)	.021*
MR	68.6 (22.6)	27	2.0 (21.4)			32	-.13.0 (20.4)		

*Statistically significant (P<.05), Manual restraint (MR), prolonged restraint (PR), p-values using independent t-tests

4.5. Safety monitoring

In total there were 19 adverse events reported across six sites. There were four that were classified as serious adverse events (admission to hospital) and 15 as non-serious adverse events.

4.5.1. Serious adverse events

The four serious adverse events (which involved three participants) were evaluated by an expert medical practitioner (AA) or the duty medical officer attached to the Primary Care and Clinical Trials Unit, University of Birmingham. They were all classified as unexpected and unlikely to have a causal relationship to the trial intervention (see Table 4.26). Three involved participants in the prolonged restraint group and one in the manual restraint group.

Table 4.26. Serious adverse events

Group allocation	Serious adverse event	Related (R) Unrelated (U)
Manual restraint	Admitted to hospital following a fit.	U
Prolonged restraint	Admitted to hospital due to a flu induced wheeze.	U
Prolonged restraint	Taken to A/E due to chest infection	U
Prolonged restraint	Taken to A/E because of a total body rash.	U

A/E Accident and Emergency department

4.5.2. Non-serious adverse events

The non-serious adverse events (n = 15) were evaluated by the assessor (PC; after unblinding) to assess the causal relationship between the intervention and the adverse event. The assessor (PC) judged that 80% (12/15) of the events should be classified as related (recognised, undesirable reaction related to the prolonged restraint). The Birmingham site reported 50% (6/12) of the related events but they also had the most participants (n = 19). Four other sites had reported events therefore it was considered they were not related to a particular site or therapist(s). The non-serious adverse events are listed in Table 4.27.

Table 4.27. Non-serious adverse events

Related (R) Unrelated (U)	Non-serious adverse event
R	Rubbing/smelly arm v
R	Bumped head which resulted in a little bruise
R	Graze on arm from wrist splint
R	Grazing and slight bruising on hand
R	Bump to the head
R	Localised eczema flare-up
R	Redness between fingers
R	Redness around the thumb
R	Redness around the thumb r
R	Redness and small area of broken skin on the hand.
R	Redness and sore, cracked skin on the hand
U	Item fell onto participant causing bruising .
U	Hip pain.
U	Raised temperature and rash.

(all participants were allocated to the prolonged restraint groups)

4.6. Discussion

4.6.1. Main findings

4.6.1.1. Assisting hand Assessment (AHA)

CIMT with a prolonged restraint methodology led to greater improvement but not a statistically significant difference in bimanual performance measured with the AHA, immediately post-intervention at ten weeks. This was compared to a manual restraint protocol. However, a within group analysis revealed both groups demonstrated a statistically significant change from baseline to ten-week assessment. The amount of improvement was greater (r = 0.5) in the prolonged restraint group compared to (r = 0.2) in the manual restraint group.

To ensure a change in score represented change in bimanual function it needed to be greater than the inherent error variance (smallest detectable difference) of the AHA. This has been calculated as five AHA-logit-based 0-100 units (Krumlinde-Sundholm, 2012). On average the change in scores in both groups at ten-week assessment represented actual change and was not due to the inherent variability evident when a repeat measurement is undertaken. The unexpected improvement in the manual restraint group may account for the non-significant difference between groups and indicated that the study was underpowered. The unexpected improvement in the usual NHS CIMT comparison group may have been influenced by the inclusion in the usual intervention of fidelity measures (diary and

questionnaire) to record the intervention delivered compared to the prescribed intervention. These would not usually be included in the NHS CIMT intervention.

4.6.1.2. Quality of upper Extremity Skills Test (QUEST)

A secondary activity measure the QUEST assessed unimanual capacity. The mean change scores across groups were not statistically significantly different. Furthermore, a within group analysis revealed that there was no difference from baseline to the ten-week assessment for both groups. This suggests that CIMT with prolonged restraint does not lead to improvement in unimanual capacity of the affected upper limb. This finding is not surprising considering CIMT primarily targets bimanual performance (Eliasson et al, 2013) and the CATCH trial was not powered to detect a difference on unimanual capacity.

4.6.1.3. Birmingham Bimanual Questionnaire (BBMQ)

The effectiveness of the intervention was measured from the perspective of the parents/guardians by asking them to complete the BBMQ a motor outcome questionnaire. It reported a statistically significant greater improvement in bimanual skill at ten weeks in the prolonged restraint group, but not maintained at the 24-week follow-up. A limitation of this assessment was that the administrators (parents/guardians) were aware of group allocation. This is particularly important because the response criteria in the BBMQ are relatively subjective. The bias associated with clinical trials that have not been appropriately blinded are that there is an overestimation of the results (Day and Altman, 2000). Although it can be argued

that because group allocation was known for both groups therefore, this problem was dealt with to a degree by randomisation.

4.6.1.4. Health related Quality of Life

HRQOL extended assessment to the subjective measures of health, including activities of daily living, which reflect participation. The PedsQL 4.0 Generic Core Scale for children (aged two years or more) combined with the PedsQL 3.0 Cerebral Palsy Module a disease specific module was administered immediately post-intervention and at the 24-week follow-up. It was inconclusive, with no statistically significant difference across groups other than between groups at baseline. Children in the prolonged restraint group measured significantly lower in their daily activity ability such as getting dressed and going to the toilet. This was not expected to impact on the study results because the intervention is not designed for a specific level of ability. Although not significant there was deterioration in the fatigue dimension in the PedsQL 3.0 CP Module in both groups immediately post-intervention. This finding could be considered in the intervention protocol of a definitive trial so that participants have rest periods implemented with a longer duration.

In younger children (less than two years of age) the PedsQL Infant scale in the manual restraint group demonstrated a statistically significant greater decline at the 24-week follow-up than the prolonged restraint group in some aspects of HRQOL. This included the summary score, psychosocial and emotional functioning of the

scale. Within group differences from baseline were investigated and revealed that in the manual restraint group there was a statistically significant deterioration at 24 weeks (not evident for the prolonged restraint group). This indicated that the manual restraint methodology may have a negative effect on aspects of the child's quality of life but this is based on small numbers and should therefore be viewed with caution. It would be useful to include HRQOL assessments in a definitive trial, to inform on both the effect of the intervention in terms of participation in daily activities and protocol development.

4.6.1.5. Safety measures

The nature of the restraint in the prolonged restraint protocol meant there was a potential for a functional deterioration in the immobilised upper limb and the occurrence of adverse events. Safety measures of the immobilised upper limb were administered (QUEST administered on the unaffected upper limb). No participant was found to have deterioration in upper limb capacity at the ten-week assessment. There were 12 non-serious adverse events related to the prolonged restraint protocol, which were either a minor skin abrasion or superficial bruising from a fall. All adverse events resolved quickly and none led to participants dropping-out. It would be expected that in this age group of children, as part of normal life children may have frequent falls causing minor bruising and skin abrasions. This suggests that the prolonged restraint protocol was safe and could be tested in a definitive trial.

4.6.2. Strengths and limitations of the research

The novel intervention investigated in the CATCH trial was considered to be complex (i.e., contain several interacting components; Medical Research Council, 2006). To help ensure that the unique challenges that this posed were addressed the trial adhered closely to the framework developed by the Medical Research Council (2006). This was throughout each phase including development, piloting and evaluation (see Figure 3.1). However, the implementation phase was not addressed in this PhD project. Additionally, it was important to ensure a complete description of this novel approach was provided both for the trial and future replication. Therefore, the Template for Intervention Description and Replication (TIDieR) checklist (Hoffmann et al., 2014) produced by a group of expert clinicians and researchers guided the descriptions.

4.6.2.1. Recruitment and follow-up

Recruitment was successfully extended from two NHS community paediatric therapy services to 16 services. The CATCH trial represents the largest investigation in the UK on CIMT in the HCP population. The multicentre nature meant a more representative population were recruited. The therapists (inexperienced researchers) approached the parents/guardians of 81 eligible participants and consent was provided for 62 children. The reasons given for non-participation were collected and could be considered in the design of a definitive trial (e.g., incorporation of attempts to keep clinic appointments to a minimum and strategies to enhance the child's independence). Although the CATCH trial consisted of a comparison group that

received usual CIMT ideally, a no intervention control group should have been incorporated. However, recruitment of participants to a third group would have been problematic.

The CONSORT guidelines (2010) were adhered to for reporting the trial. Ninety seven percent (60/62) of participants completed the ten-week assessment and 95% (59/62) at 24 week follow-up, which demonstrated excellent retention. Measures had been put in place to enhance retention, for example, it had been anticipated that the participants randomised to the manual restraint group may be disappointed and drop out therefore, they were offered an episode of prolonged restraint on trial exit. In addition, although administration of the intervention under investigation was primarily conducted by parents/guardians the burden was minimised because therapists were responsible for application of the prolonged restraint. The recruitment and retention rates from the CATCH pilot trial suggest that it was feasible and enhanced estimation of likely rates of recruitment and retention for a definitive trial.

4.6.2.2 Randomisation and allocation concealment

Randomisation stratified by site aimed to maintain similarity between groups at baseline both for participants and for the intervention administration. The allocation sequence was protected prior to randomisation by the generation of an unpredictable computer generated allocation sequence. This was unknown to the intervention therapists presenting patients for allocation or the assessor. Evaluation at baseline revealed that randomisation was successfully conducted with little difference in

participant characteristics between groups, providing some assurance that the results were not influenced by factors other than the intervention (Sedgwick, 2014). Consideration needs to be given to factors which have not been measured that may affect the intervention such as parental compliance. However, the size of the sample size should minimise the effects.

4.6.2.3. Blinding

Evaluation of the outcomes in the CATCH trial was conducted by a blinded assessor and inadvertent unblinding occurred in three participants and group allocation was correctly guessed for another two. Therefore, the assessor was aware of group allocation for 8% (5/60) of participants. It is difficult to gage an acceptable level of blinding because of the small number of trials that report on blinding performance (Hróbjartsson et al., 2007). However, blinding was considered a limitation in the trial and discussed further in Chapter 9.

4.6.2.4. Use of outcome measures

Assisting hand Assessment

The spread of the mean change in AHA scores at the ten-week assessment across groups was investigated by displaying them on a box and whisker diagram. There were a number of outliers (four in the manual and two in the prolonged restraint group) suggesting extreme change which were unexpected. The most extreme case

indicated a large improvement in the manual restraint group. It was investigated by observation of the AHA video assessments. This revealed the child (who was less than two years old) was uncooperative at both assessment time point, but perhaps was more so at baseline. Removal of this case improved the findings to demonstrate almost a statistically significant difference in mean change scores across groups. An explanation for the unexpectedly large improvement at the ten-week assessment was associated with cooperation rather than upper limb ability. This suggests a possible discriminatory limitation in the AHA. It could be argued that the assessment should have been repeated at a time when the child was more cooperative and the upper limb motor ability was stable. This was not possible because of resource implications.

The CATCH study design used a randomisation methodology for group allocation hence children with poor cooperation could have equally been allocated to either group. Indeed, at baseline co-operation was compared across groups and found to be similar ($p = .346$).

Poor discrimination can be considered a limitation however, it would be recommended that the AHA is used for a full-scale trial but, it is imperative that group allocation is conducted by a method of randomisation. Furthermore, in a full-scale trial there needs to be a facility to repeat assessments if required within a time-frame that the upper limb would be expected to be stable. In addition, a larger sample size in a definitive trial would reduce the impact of the extreme values represented by the outliers.

Birmingham Bimanual Questionnaire

The parent-reported BBMQ assessment at 24 weeks (a secondary outcome measure) was the only motor assessment of the long-term motor effects of the interventions. A definitive trial would need to be appropriately financed to allow blinded assessment both immediately post-intervention and on long–term follow up. The majority of 24 week postal assessments were completed but there was discrepancy between planned and actual timings of the assessment. The late-return of the 24 week assessments prompted the offer of an incentive (£10.00 gift voucher offered on their return). Although this was considered ethical as parents/guardians had already consented it does suggest that there was difficulty with the completion and return of the 24-week postal self-reported questionnaires. Therefore, postal self-reported administration of assessments would not be recommended for future studies. The late return may have impacted on the assessments especially because of the effects of maturation and change in motor skills. However, both groups demonstrated a similar time delay in their return therefore, both groups affected similarly.

4.6.3. Related research

The CATCH trial was combined in a systematic review and meta-analysis with relevant trials from an existing Cochrane systematic review (Hoare et al., 2007) and

any new controlled studies. This allowed the possibility of comparison and synthesis with other studies and is reported in Chapter 8.

4.6.4. Clinical implications

It would seem reasonable in view of the greater treatment effects, safety of the intervention and acceptability to families that a prolonged restraint methodology should be considered as a promising intervention and replace usual CIMT methodology. Although, it is recommended that further research is required to support implementation especially in terms of long term outcomes and cost effectiveness.

4.6.5. Research implications

The CATCH trial closely followed the guidelines provided by the Medical Research Council (2006) to guide researchers to develop and evaluate complex interventions. The implementation stage was not included however the trial has provided invaluable information for a future definitive trial. The intervention outcomes can be used to power a full-scale trial. In addition, the successful application of trial procedures including interventions, assessments, randomisation, allocation concealment and blinding provide guidance for future investigation. The excellent recruitment and retention rates support feasibility for a full-scale investigation and the greater treatment effects of the novel approach and safety outcomes suggest it should be tested in a definitive trial.

4.7. Conclusion

The CATCH trial was conducted to determine the efficacy of a novel approach to CIMT with a prolonged restraint methodology for pre-school children with HCP. It was compared to usual NHS CIMT and both groups changed immediately post-intervention and although there was not a statistically significant group difference, the prolonged restraint methodology resulted in a greater treatment effect. The unexpected improvement in the comparator group was a limitation and suggests that the CATCH trial was underpowered. Therefore, in a definitive trail a no-treatment comparator group recommended. Furthermore, inadvertent unblinding of the assessor to group allocation for 8% of participants may have resulted in bias although, this finding could be used to inform the design of a future investigation.

The feasibility of conducting a RCT within an NHS community paediatric environment was evaluated in order to assess and revise the design for a definitive trial. The excellent retention of participants on the trial indicated that families found it acceptable. Therefore, a definitive trial to investigate this novel approach to CIMT is feasible and the greater treatment effect provides sufficient justification to plan a larger multi-centre trial appropriately powered for both short and longer term outcomes and to provide an economic analysis.

The CATCH trial should inform the design of a definitive trial however, more information from the parents/guardians and nursery workers who administered the

interventions was required. To record this we asked them and the nursery workers to complete two data collection tools, which will be described in the next chapter.

Chapter 5: Parent and nursery worker reported outcomes on fidelity to constraint induced movement therapy in the CATCH trial

5.1. Introduction

The randomised controlled trial reported in this thesis compared two methods of constraint induced movement therapy (CIMT) to improve functional ability in the affected upper limb in pre-school children with hemiplegic cerebral palsy (CATCH). The CIMT interventions under investigation were a novel approach with prolonged restraint compared to a NHS CIMT intervention used in standard clinical practice. The interventions were predominately administered by the parents/guardians and nursery workers, in the child's home or nursery environment. Fidelity to treatment includes the appraisal of a treatment intervention in terms of what was actually delivered compared to what was intended (Carroll et al., 2007). Without an understanding of the actual intervention delivered, accurate conclusions about treatment efficacy cannot be made and interventions cannot be replicated (Bellg et al., 2004). Therefore, measurement of the therapy delivered and the child's cooperation with the restraint was quantified by parents/guardians and nursery workers using two data collection tools.

5.2. Aims of the study

The aims of the study reported in this chapter were to compare the fidelity of treatment across groups in the CATCH trial. Furthermore the association between the two data collection tools administered in the home environment will be reported. Measures to enhance the CIMT delivered with prolonged restraint will be considered.

5.3. Methods

This study is part of a larger project (CATCH trial) whose aims were to determine the feasibility and short-term efficacy of a novel approach of CIMT and to provide sufficient justification to plan a definitive trial. The methodology of the CATCH trial is outlined in Chapter 3. The Template for Intervention Description and Replication (TIDieR) checklist (Hoffmann et al., 2014) produced by a group of expert clinicians and researchers guided the descriptions and analysis of the fidelity measures adhered to in the CATCH trial. The measures were outlined in terms of how they were applied and by whom and analysed according to the extent to which the intervention was delivered as planned.

The fidelity measures included two data collection tools (see Table 5.1). A paper based daily diary which asked the parent/guardian and nursery worker two close-ended questions with pre-determined responses about the daily fidelity to treatment in the home or nursery. In addition, the parent/guardian and nursery worker was interviewed by the intervention therapist (responsible for the CATCH trial) and asked

about fidelity to treatment over the previous week. The therapist used a questionnaire which included the same two close-ended questions with pre-determined responses that were in the daily diary. It was administered either face-to-face or by telephone. One of the questions asked about the proportion of the prescribed 60 minutes of daily therapy that had been delivered. The second question asked how cooperative the child had been with the restraint (see Appendix 5 for a script of the dairy and questionnaire for home).

Table 5.1. Methods of data collection

	Daily diary	Parent questionnaire	Nursery daily diary	Nursery questionnaire
Respondent	Parent/ guardian	Parent/ guardian	Nursery worker	Nursery worker
Environment	Home	Home	Nursery	Nursery
Method of administration	Self-completion	By therapist	Self-completion	By therapist
Format	Paper	Telephone/ face-to-face	Paper	Telephone/ face-to-face
Response type	Pre-determined	Pre-determined	Pre-determined	Pre determined
Frequency	Daily	Weekly	Daily	Weekly

5.3.1. Data analysis

Initially the data were examined for response rates and missing data and this was described using percentages and numbers. The pre-determined responses for the two questions were the same for the daily diary and questionnaire. The daily diary reported on treatment fidelity for each day whereas the questionnaire related to the previous week. The responses to the question on amount of therapy delivered over a period of time were numerically coded to allow statistical analysis and more therapy meant a higher score. The scores were as follow;

- “hardly at all” (scored one)
- “less than 30 minutes” (scored two)
- “for 30 minutes” (scored three)
- “nearly 60 minutes” (scored four)
- “all 60 minutes” (scored five)

Additionally, the administrators of the intervention were asked about the child’s cooperation with the restraint with a higher score indicating more cooperation. The responses and scores were;

- “never” (scored one)
- “seldom” (scored two)
- “about half the time” (scored three)
- “usually” (scored four)
- “always” (scored five)

The mean daily responses were calculated after the missing responses had been removed. Frequency distributions were used to display and visually assess the data. To summarise the dispersion of typical values across groups, the data was presented in box-plots which identified the quartiles and outliers for the mean daily responses across groups. The box-plots were not normally distributed, and therefore a Mann Whitney U Test compared the group medians (Field, 2009). To test the agreement between the techniques for individual cases the relationship between the daily diary and the parent questionnaire collecting the same data from the home environment were examined with the Bland and Altman method (1986).

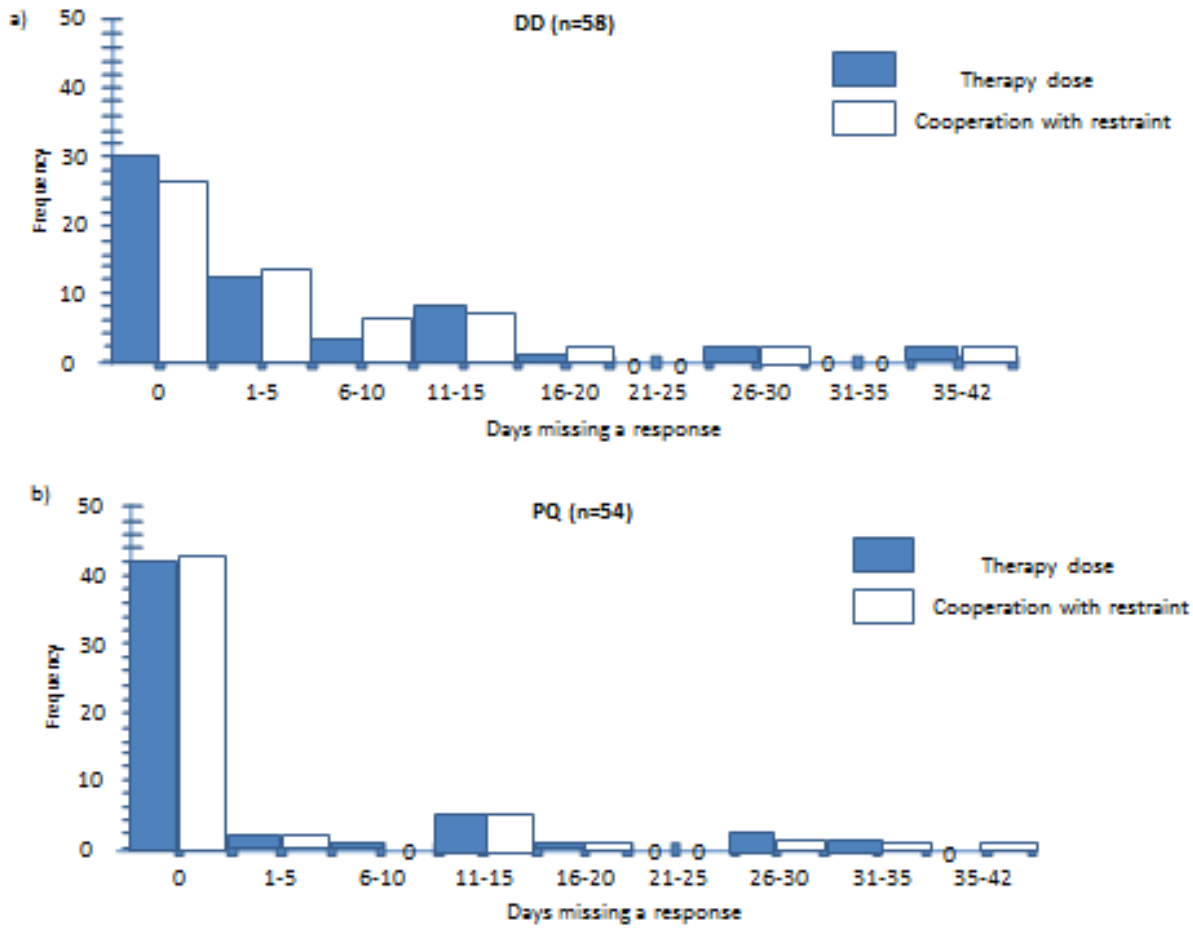
5.4. Results

5.4.1. Response rates and missing data

Sixty-two participants were enrolled into the study and there was a 94% (58/62) response rate for the daily diaries and 87% (54/62) for the parent questionnaires.

Two diaries provided no information on dose. In the remainder (27 from the manual restraint group and 29 from the prolonged restraint group), information was complete on dose for 30 cases and in 26 cases there was between 1 to 27 days missing a response. For cooperation with the restraint, one diary provided no information but for the remaining 57 diaries, there were 26 diaries that were complete but 31 diaries had between 1 and 41 days with no response. The frequency of days missing a response for each question in the daily diary is shown in Figure 5.1a.

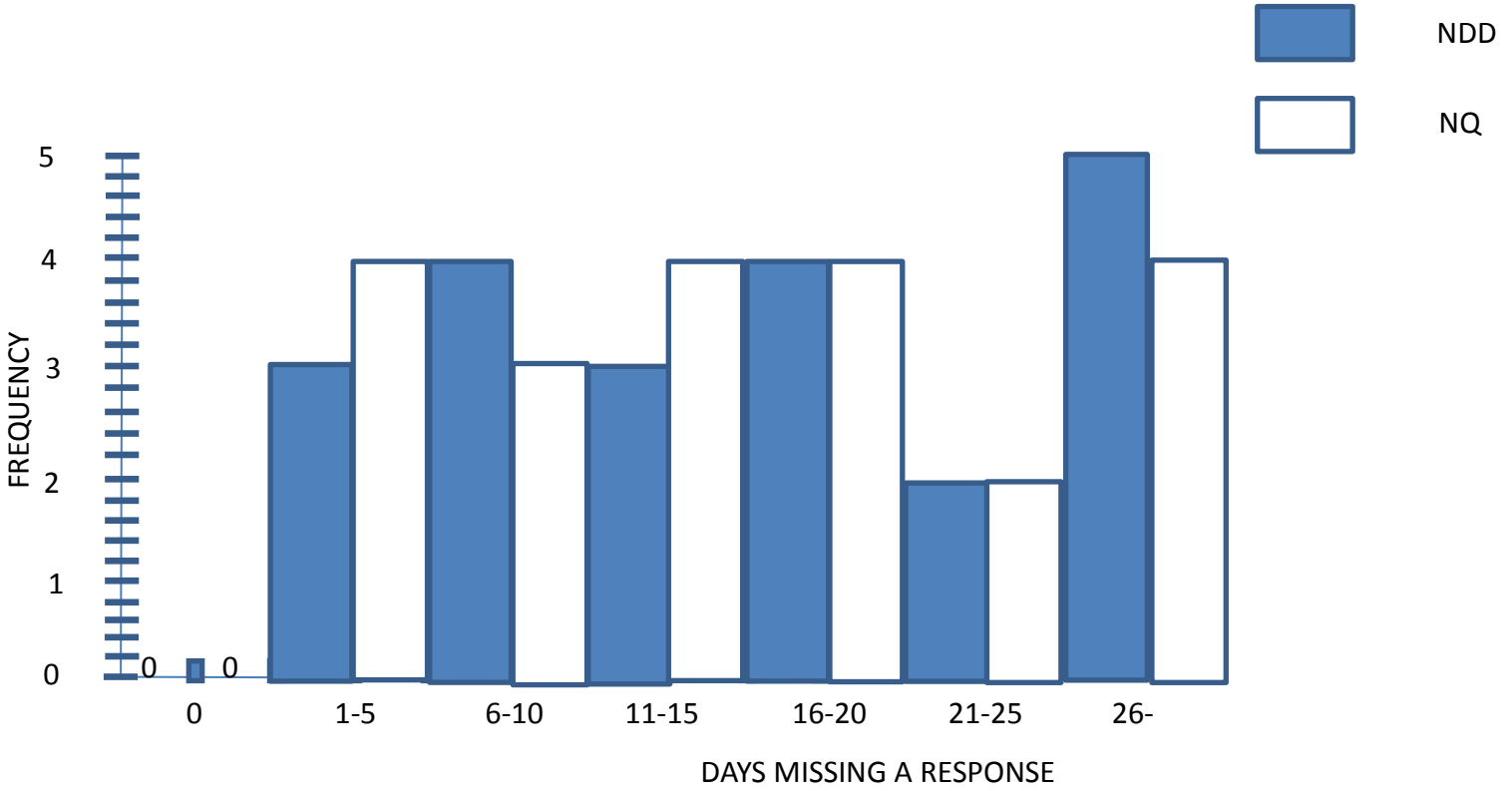
All of the 54 returned parent questionnaires had a response about therapy dose (26 from the manual restraint group and 28 from the prolonged restraint group). Fifty-three cases responded about cooperation with the restraint (26 from the manual restraint group and 27 from the prolonged restraint group) and one provided no information. Returned parent questionnaires that reported dose were complete for every day in 42 cases (6 weekly reports) and 12 cases had between 1 and 32 days missing a response. There were 43 parent questionnaires reporting cooperation which had no missing data however 10 cases had between 2 and 32 days missing a response. Figure 5.1b shows the amount of days missing a response for both questions in the parent questionnaires. The data for days missing a response for both the diaries and the questionnaires has been presented in a bar chart format to allow a within tool comparison for each question and a comparison across the tools.



DD (daily diary) PQ (parent questionnaire)

Figure 5.1. Frequency of days missing a response for dose and cooperation with restraint in the returned daily diary and parent questionnaire.

Twenty five of the 62 participants enrolled into the study attended a nursery and of those there were 21 participants (84%) about whom data had been returned. This included 10 from the manual restraint group and 11 from the prolonged restraint group. If data from the nursery had been returned, it was always completed for both questions in each data collection tool therefore, the response rate for the tool rather than individual questions was presented. The returned data from the nursery may have consisted of both a nursery daily diary and a nursery questionnaire (n = 16), only a nursery diary (n = 2) or only a nursery questionnaire (n = 3). If the child attended nursery full time, the maximum amount of days that could be completed was 30 days (i.e. weekends were excluded). However many of the children attended nursery part time. None of the nursery diaries or questionnaires was completed for all 30 days. There were between 2 and 30 days missing a response in the nursery daily diaries and between 1 and 30 days in the nursery questionnaires. Figure 5.2 shows the amount of days missing a response (combined questions) in the nursery questionnaire and in the nursery diary and presented in a bar chart format to allow a comparison of days missing a response across tools.



NDD (nursery daily diary) NQ (nursery questionnaire)

Figure 5.2. Frequency of days missing a response in both the nursery daily diary and nursery questionnaire (n = 21)

5.4.2. Between group comparison

In this section, data from the daily diaries, parent's questionnaires, nursery daily diaries and nursery questionnaires were compared between groups. The data on therapy dosage reported in the daily diaries is presented in Figure 5.3. In the prolonged restraint group it was negatively skewed (z-score of skewness = -1.69) compared to the more symmetrical data of the manual restraint group (z-score of skewness = -0.154) which indicated more participants in the prolonged restraint group, received more therapy. Furthermore, the median amount of therapy delivered in this group was greater and less dispersed (i.e., the interquartile range (IQR) was "for 30 minutes" and "all 60 minutes" whereas the manual restraint group reported "less than 30 minutes" to "nearly 60 minutes". The group medians were compared and the amount of therapy delivered in the prolonged restraint group (Median = 4.1, IQR 1.5) was statistically significantly higher than in the manual restraint group (Median = 3.1, IQR 2.0; $U = 223$, $z = -2.8$, $p < 0.01$).

The data for cooperation with prolonged restraint measured on the daily diaries is shown in Figure 5.4. It demonstrated similar findings to the data on dosage (i.e., the data was negatively skewed in the prolonged restraint group (z-score of skewness = -3.099) compared to the manual restraint group (z-score of skewness = -0.866)). This suggests more participants in the prolonged restraint group showed greater cooperation. The median amount of cooperation was greater in this group with less dispersion of scores. The IQR for cooperation in the prolonged restraint group was reported as between "about half the time" to "always" whereas in the manual restraint

group it was “seldom” to “usually”. The median amount of cooperation across groups was compared. The prolonged restraint group (Median = 4.4, IQR 1.4) was statistically significantly higher compared to the manual restraint group (Median = 3.3, IQR 1.9; U =145, z = - 4.2, $p<0.01$).

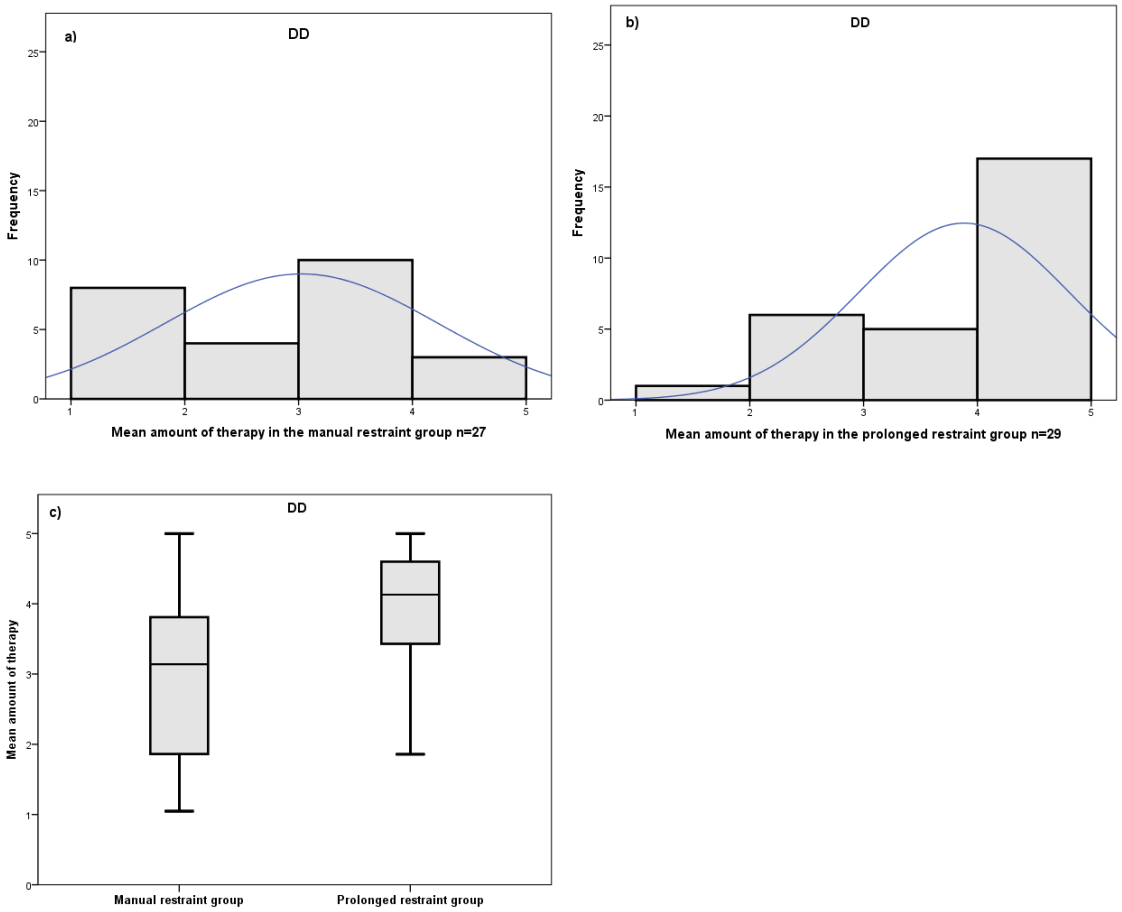
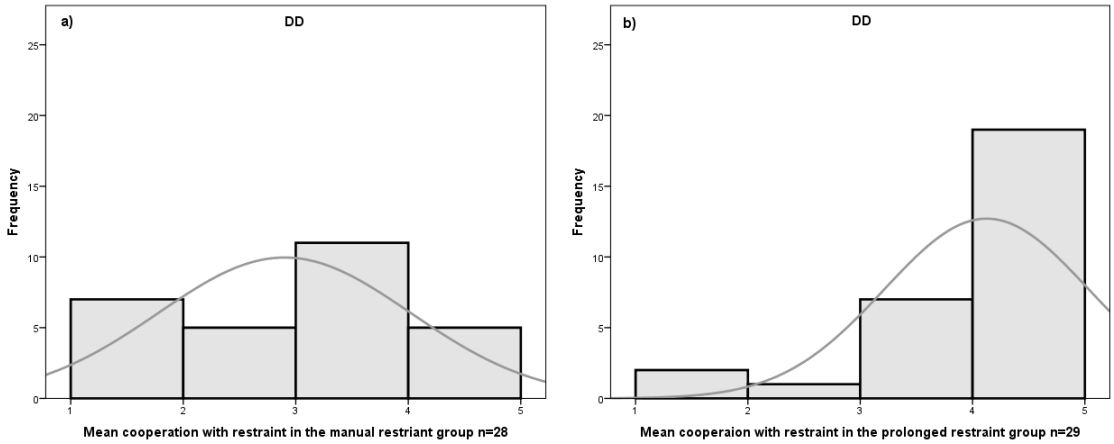


Figure 5.3. Frequency distribution and box plot of mean dose of therapy between groups measured with the daily diaries
(1 = “hardly at all”, 2 = “less than 30 minutes”, 3 = “for 30 minutes”, 4 = “nearly 60 minutes”, 5 = “all 60 minutes”, DD = daily diary)



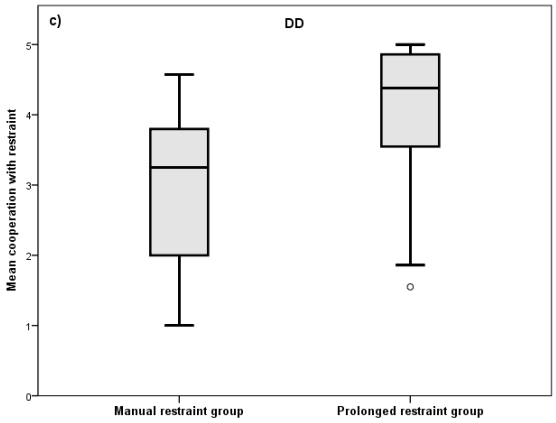


Figure 5.4. Frequency distribution and box plot of mean cooperation with the restraint between groups measured with the daily diaries
(1 = “never”, 2 = “seldom”, 3 = “about half the time”, 4 = “usually” 5 = “always”, DD = daily diary)

The data recorded with the parent questionnaires for the therapy dose (Figure 5.5.) and cooperation with the restraint (Figure 5.6.) showed a similar trend to that reported by the daily diaries. The data for therapy dose in the prolonged restraint group were negatively skewed (z-score of skewness = -1.146) compared to the more symmetrical data (z-score of skewness = -0.654) from the manual restraint group. This indicated more participants received a higher dose in the prolonged restraint group. The median amount of therapy delivered in the prolonged restraint group was higher and less dispersed (the IQR in the prolonged restraint group was between “for 30 minutes” and “all 60 minutes” whereas the manual restraint group reported “less than 30 minutes” to “nearly 60 minutes”). The group medians were compared and in the prolonged restraint group, (Median 4.2, IQR 0.9) was statistically significantly higher than in the manual restraint group (Median = 3.6, IQR 1.3; $U = 155$, $z = -3.7$, $p < 0.001$). Similarly, the data (see Figure 5.6.) was negatively skewed on cooperation in the prolonged restraint group (z-score of skewness = -2.746)compared to the the manual restraint group (z-score of skewness = 1.296). The median amount of cooperation was greater and less dispersed. The IQR in the prolonged restraint group for cooperation was “about half the time” to “always” whereas in the manual restraint group it was “seldom” to “usually”. When compared across groups, the prolonged restraint group for cooperation (Median = 4.7, IQR 1.0) was statistically significantly greater than in the manual restraint group (Median = 3.0, IQR 1.7; $U = 111$, $z = -4.3$, $p < 0.001$).

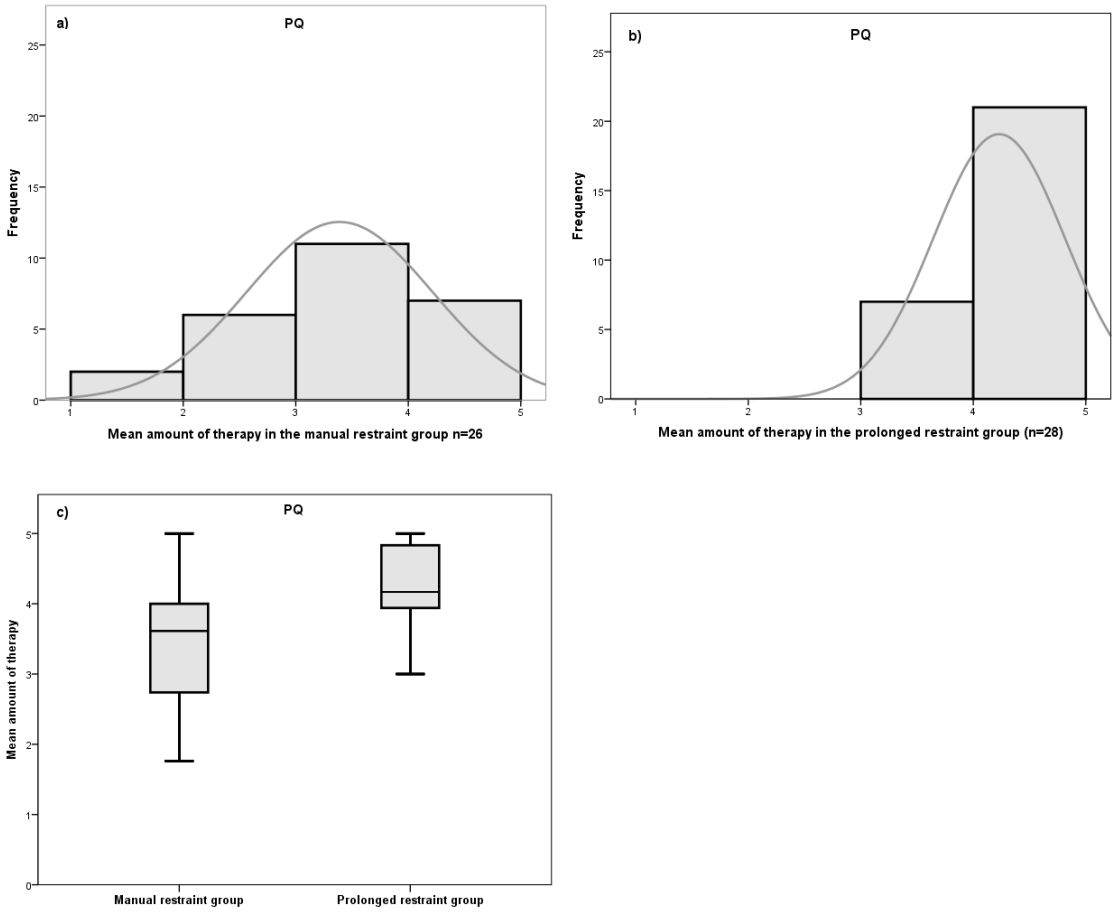
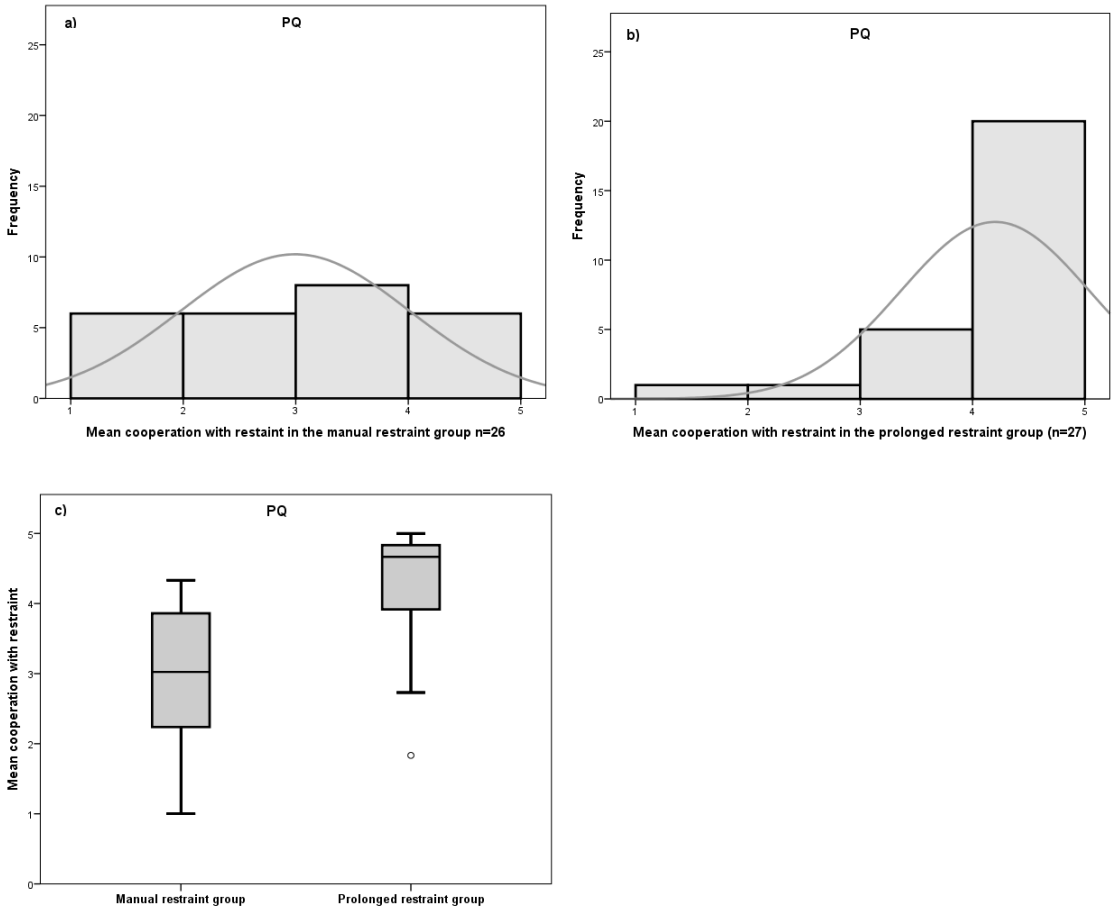


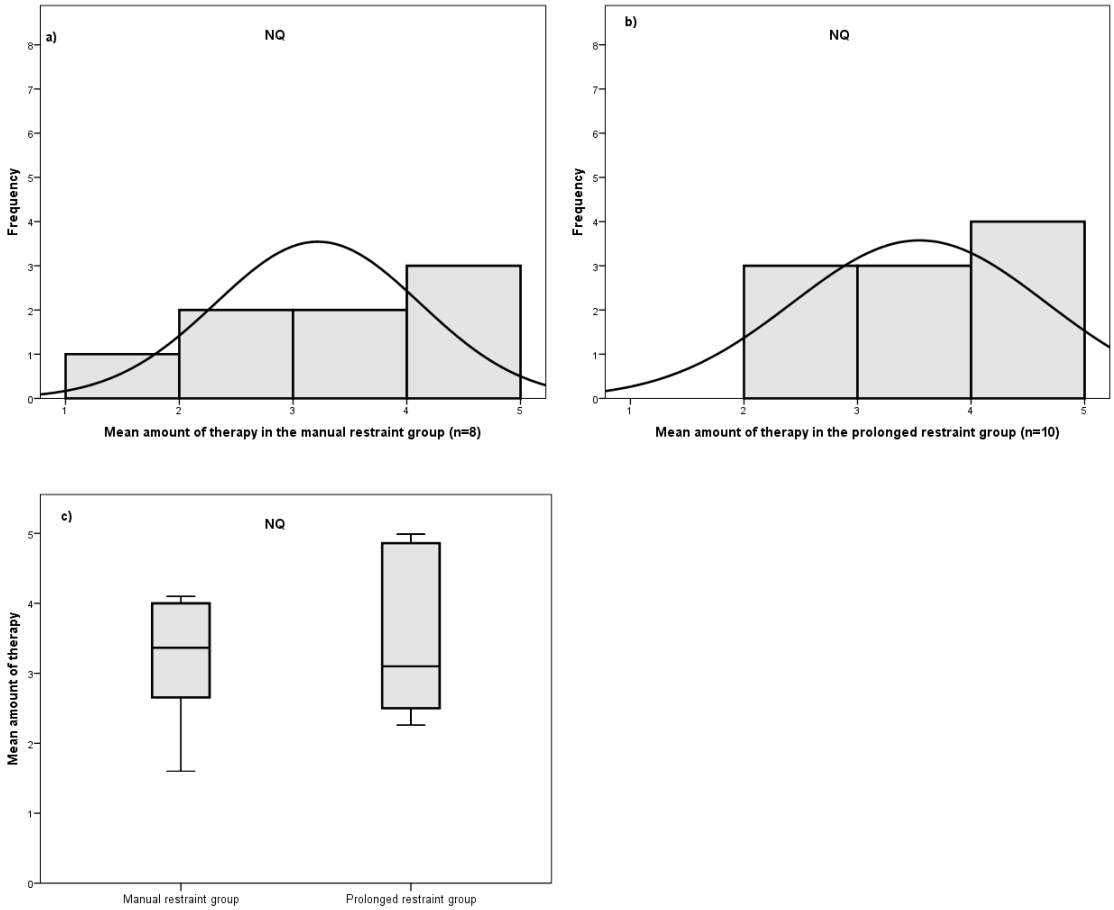
Figure 5.5. Frequency distribution and box plot of mean therapy dose between groups measured with the parent questionnaire
(1 = “hardly at all”, 2 = “less than 30 minutes”, 3 = “for 30 minutes”, 4 = “nearly 60 minutes”, 5 = “all 60 minutes”, PQ (parent questionnaire)



PQ (parent questionnaire)

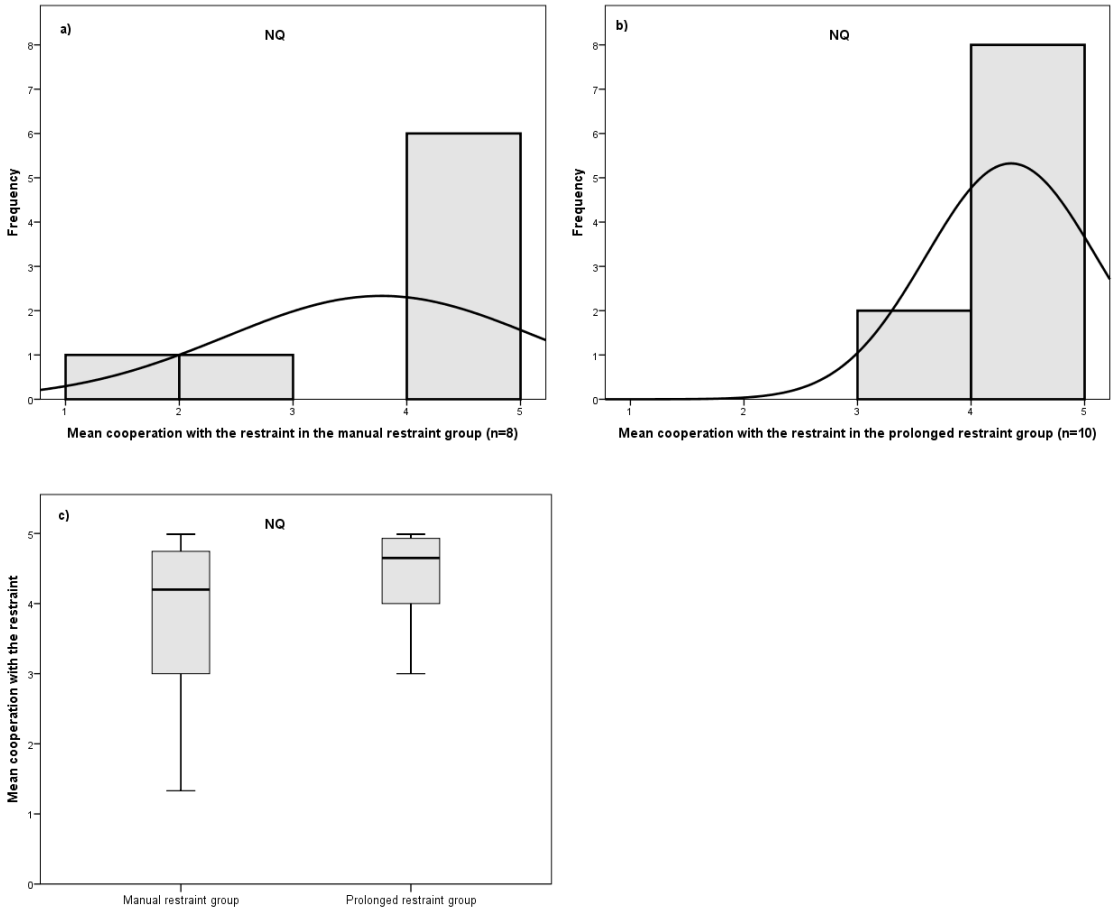
Figure 5.6. Frequency distribution and box plot of mean cooperation with the restraint between groups measured with the parent questionnaire
(1=“never”, 2 = “seldom”, 3 = “about half the time”, 4 = “usually” 5 = “always”, PQ (parent questionnaire)

Display of the data retrieved from the nursery (measured with the nursery questionnaire) demonstrated a different finding to that reported by the parents/guardians (see Figure 5.7). The distributions of data on therapy dosage were both relatively symmetrical. The z-score of skewness = 0.477 for the prolonged restraint group and -0.104 for the manual restraint group suggesting a range of dosage was delivered to both groups. The median amount of therapy delivered in the prolonged restraint group was slightly lower (Median = 3.1, IQR 2.4) but similar to the manual restraint group (Median = 3.4, IQR 1.5; U = 47, p = 0.573). The variability was the same in both groups (IQR was reported as “less than 30 minutes” to “nearly 60 minutes”). The negatively skewed data on cooperation with the restraint for both groups (i.e., z-score of skewness = -1.606 for the prolonged restraint group and -1.585 for the manual restraint group; see Figure 5.8) indicated that participants in both groups were cooperative. The medians were compared and cooperation with the restraint in the prolonged restraint group (Median = 4.7, IQR 1.1) was similar to the manual restraint group (Median = 4.2, IQR 2.4, U = 48.5, p = 0.46). Additionally, the IQR in both groups was the same and reported as “about half the time” to “always”.



NQ (Nursery questionnaire)

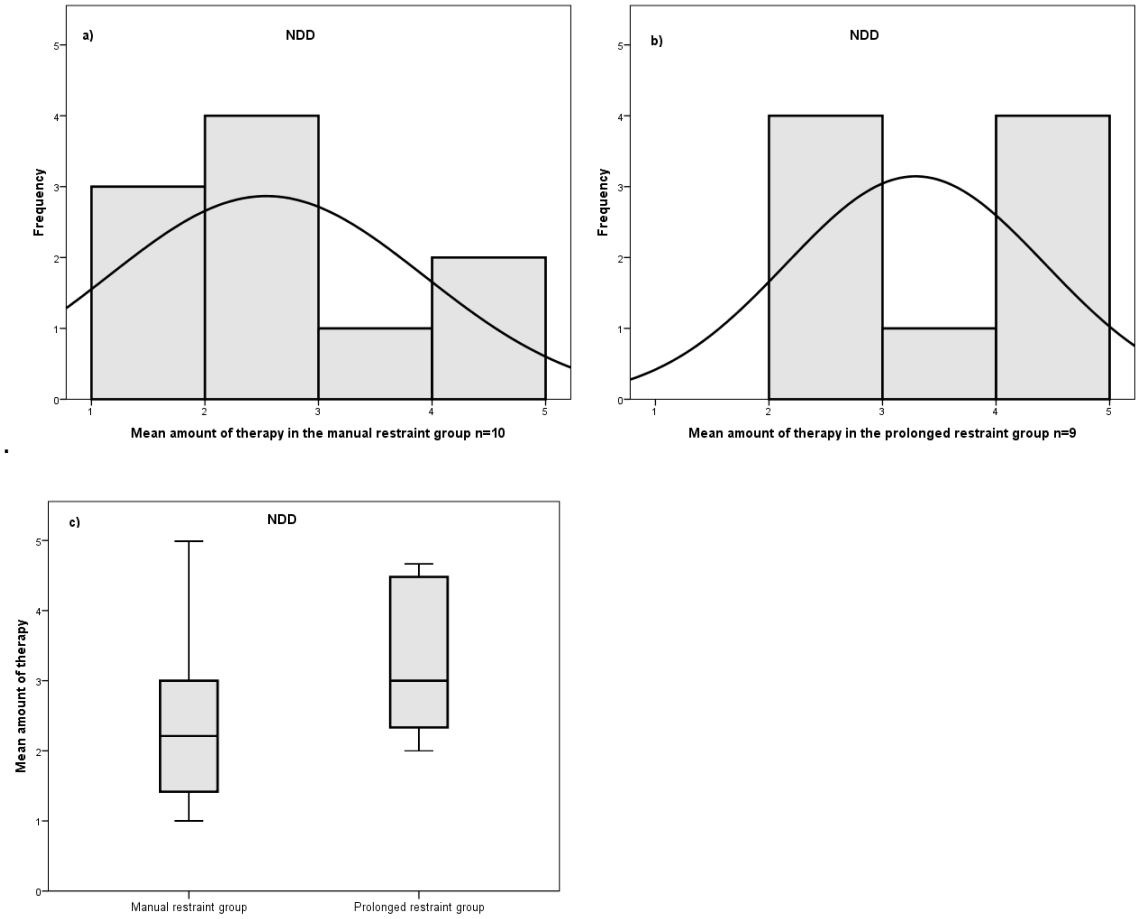
Figure 5.7. Frequency distribution and box plot of the therapy dose at nursery between groups measured with the nursery questionnaire
(1 = “hardly at all”, 2 = “less than 30 minutes”, 3 = “for 30 minutes”, 4 = “nearly 60 minutes”, 5 = “all 60 minutes”, NQ (nursery questionnaire)



NQ (Nursery questionnaire)

Figure 5.8. Frequency distribution and box plot of the mean cooperation with the restraint at nursery between groups measured with the nursery questionnaire (1 = “never”, 2 = “seldom”, 3 = “about half the time”, 4 = “usually” 5 = “always”, NQ = nursery questionnaire)

The data recorded with the nursery daily diary for the amount of therapy (see Figure 5.9) in the prolonged restraint group showed a symmetrical distribution (z-score of skewness = 0.188) compared to a more positive skew in the manual restraint group (z-score of skewness = 1.467), indicating lower scores in the latter group.. The median amount of therapy delivered in the prolonged restraint group (Median = 3.0, IQR 2.4) was similar to the manual restraint group (Median = 2.2, IQR, 2.1 U = 59.0, p = 0.243). However, the dispersion was different. The IQR in the prolonged restraint group was “hardly at all” to “for 30 minutes” and for the manual restraint group was “less than 30 minutes” to “all 60 minutes”. The distribution of data on cooperation with the restraint across groups measured with the nursery daily diary was skewed negatively in the prolonged restraint group (z-score of skewness = -1.222) and more symmetrically in the manual restraint group (z-score of skewness = -0.460). See Figure 5.10. This suggested that the participants in the prolonged restraint group were more cooperative. However, the group medians were compared and cooperation in the prolonged restraint group (Median = 4.0, IQR 1.3) was found to be similar to the manual restraint group (Median = 3.9, IQR 2.2, U = 45.0, p = 1.0). Furthermore, variability of the scores on cooperation was similar and scored at between “seldom” and “usually”.



NDD (nursery daily diary)

Figure 5.9. Frequency distribution and box plot of the mean amount of therapy at nursery between groups measured with the nursery daily diary
(1 = “hardly at all”, 2 = “less than 30 minutes”, 3 = “for 30 minutes”, 4 = “nearly 60 minutes”, 5 = “all 60 minutes”, NDD (nursery daily diary)

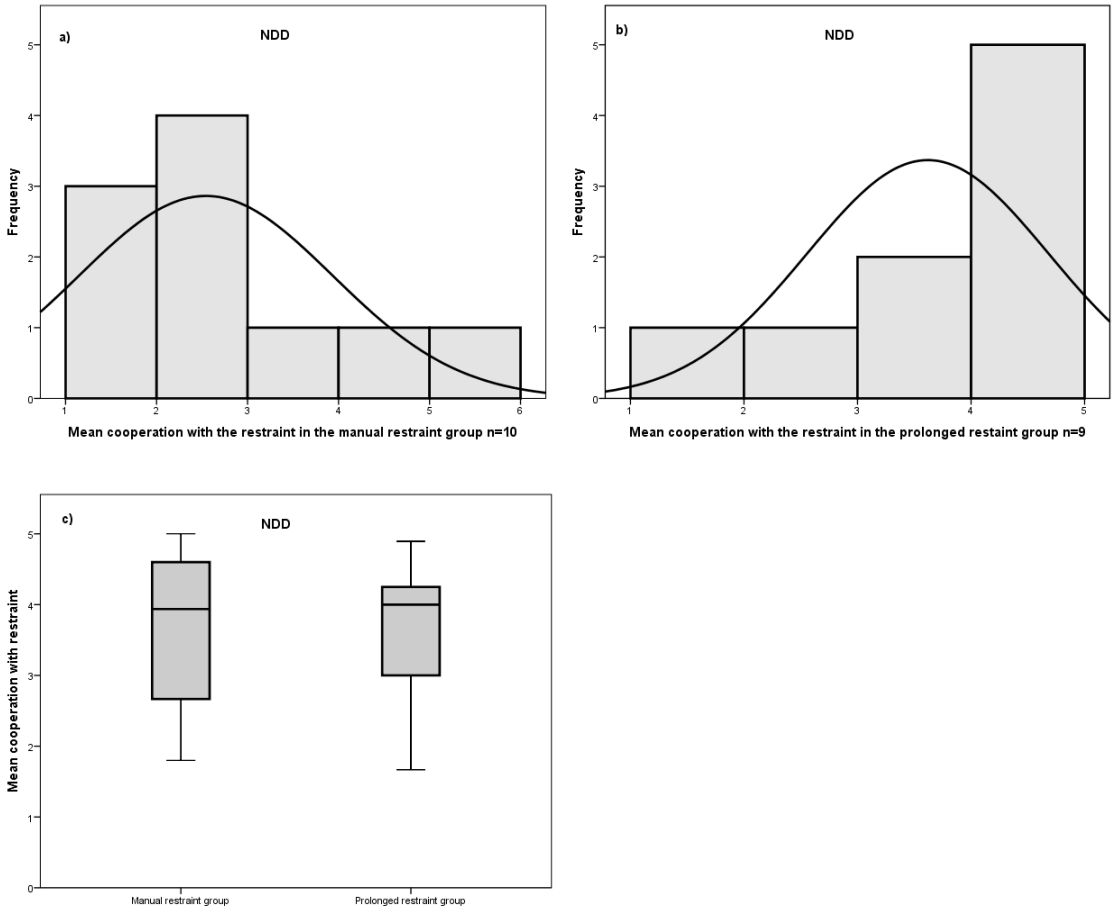


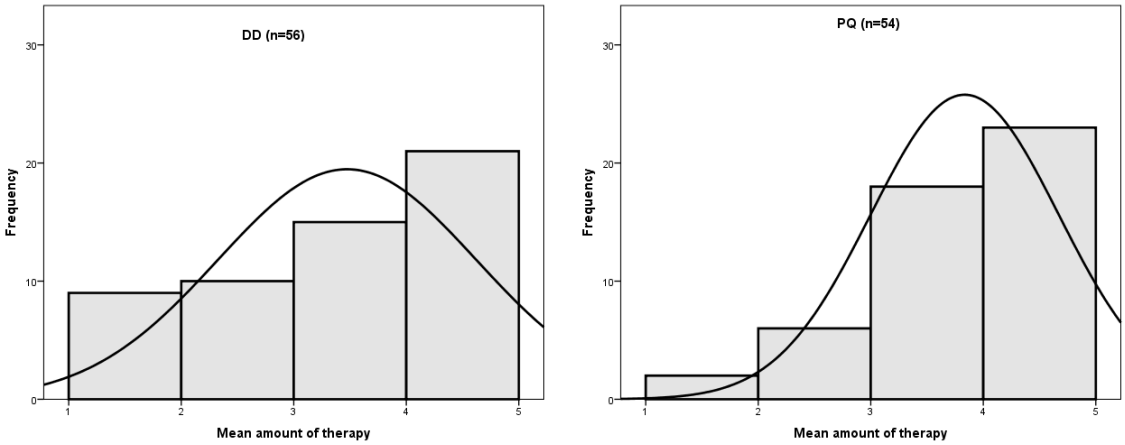
Figure 5.10. Frequency distribution and boxplot of the mean cooperation at nursery between groups measured with the nursery daily diary
(1 = “never”, 2 = “seldom”, 3 = “about half the time”, 4 = “usually” 5 = “always”, NDD = nursery daily diary)

5.4.3. Comparison between methods of parent/guardian data collection

A comparison was made between the two data collection tools (daily diary and a weekly parent questionnaire) used to collect data about parent/guardian administered therapy. The mean scores of therapy dose and cooperation to the restraint recorded from each method were compared.

5.4.3.1. Therapy dose

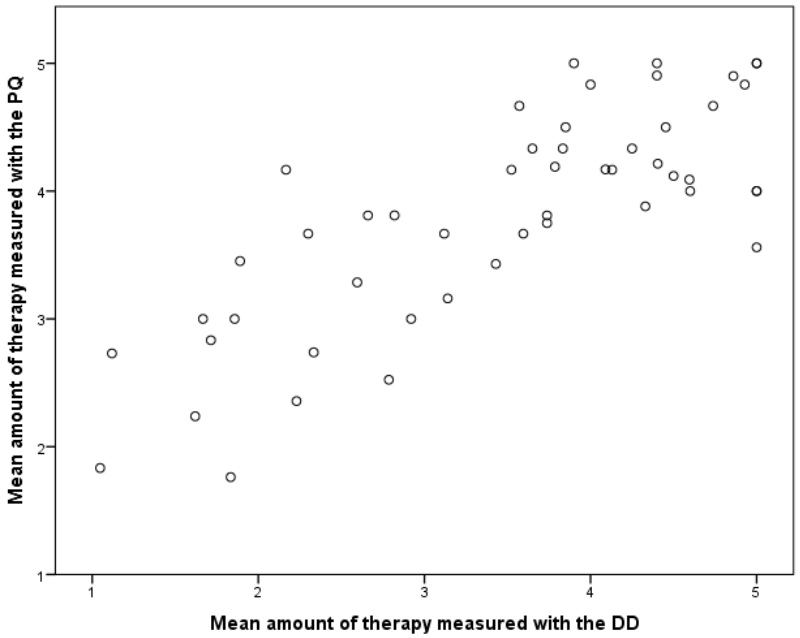
The similarity between the frequency distributions of the scores on therapy dose measured using the diary compared to the questionnaire shown in Figure 5.11, suggest they were measuring a comparable attribute. The negative skew on both the diary and questionnaire (z-scores of skewness = -1.467 and -1.862 respectively) which indicated more participants received a higher dose. Furthermore, the scatterplot (Figure 5.12.) demonstrated a high positive correlation (r_s = 0.74).



DD (daily diary) PQ (parent questionnaire)

Figure 5.11. Frequency distributions of the daily diary and parent questionnaire on therapy dose

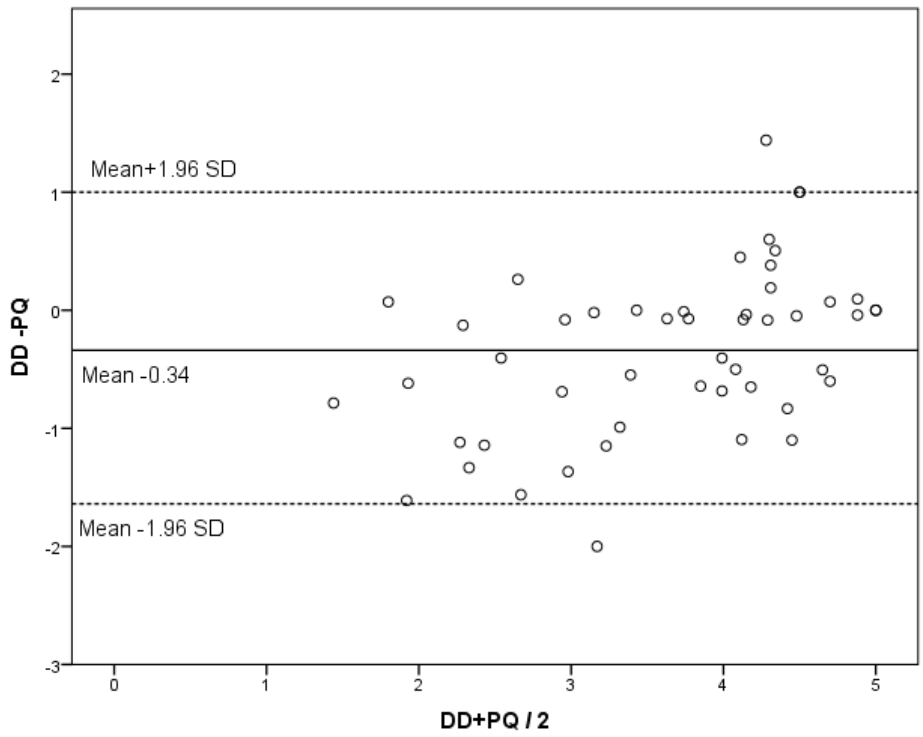
.



DD (daily diary) PQ (parent questionnaire)

Figure 5.12. Correlation between therapy dose scores on the daily diary and parent questionnaire

A Bland and Altman (1986) method was used to calculate the mean difference across data collection methods for individual cases. Participants with a missing daily diary (6 cases) or parent questionnaire (8 cases) were excluded and given that 2 cases had a daily diary and a parent questionnaire missing a total of 12 cases were omitted from the analysis. On average the parent questionnaires tended to overestimate the therapy dose by 0.34 with a standard deviation of 0.7. The limits of agreement lie between - 1.68 and 1.03 as shown in the Bland-Altman plot in Figure 5.13 and in Table 5.2.



DD (daily diary) PQ (parent questionnaire)

Figure 5.13. Bland-Altman plot (daily diary versus parent questionnaire scores for the therapy dose scores.

Table 5.2. Daily diary versus parent questionnaire scores for therapy dose scores

Measure	n	Mean difference	SD	95% limits	Lower CI	Upper CI	Tendency
DD-PQ	50	- 0.34	0.7	1.34	-1.68	1.03	PQ > DD

DD (daily diary) PQ (parent questionnaire)

The confidence intervals were calculated to be between – 0.51 and -0.15, which indicates that on average the parent questionnaire score could be between - 0.5 and - 0.1 higher for therapy dose compared to the daily diary.

5.4.3.2. Cooperation with restraint

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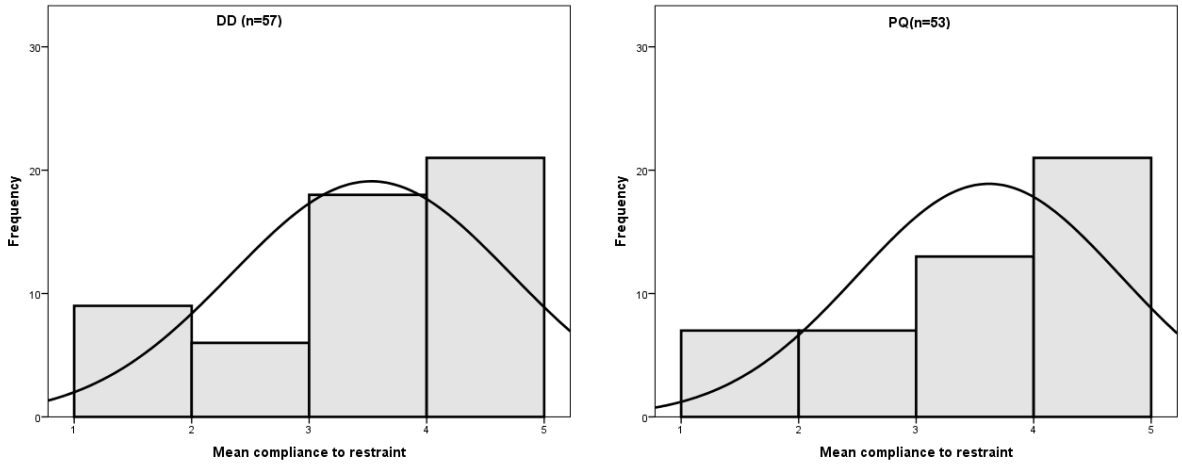

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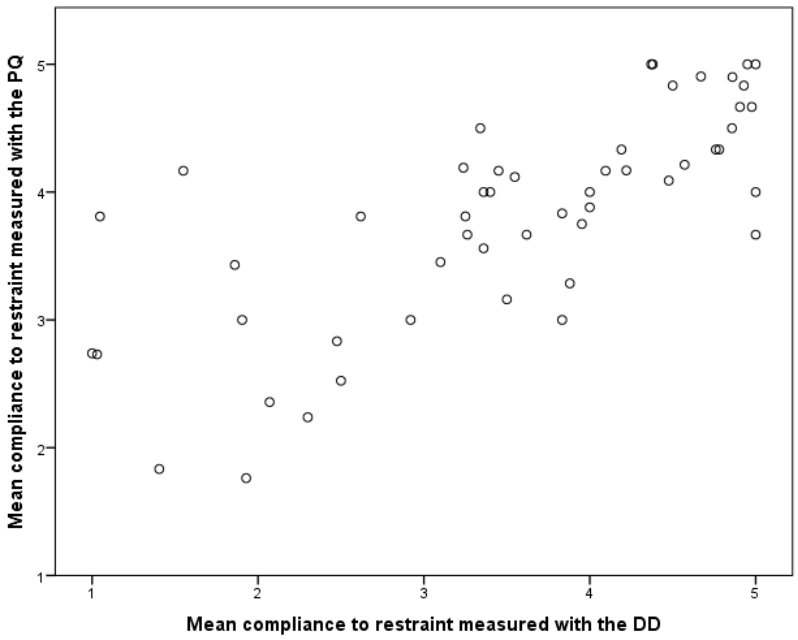
DD (daily diary) PQ (parent questionnaire)

Figure 5.14. Frequency distributions of the cooperation with restraint measured using the DD and the PQ

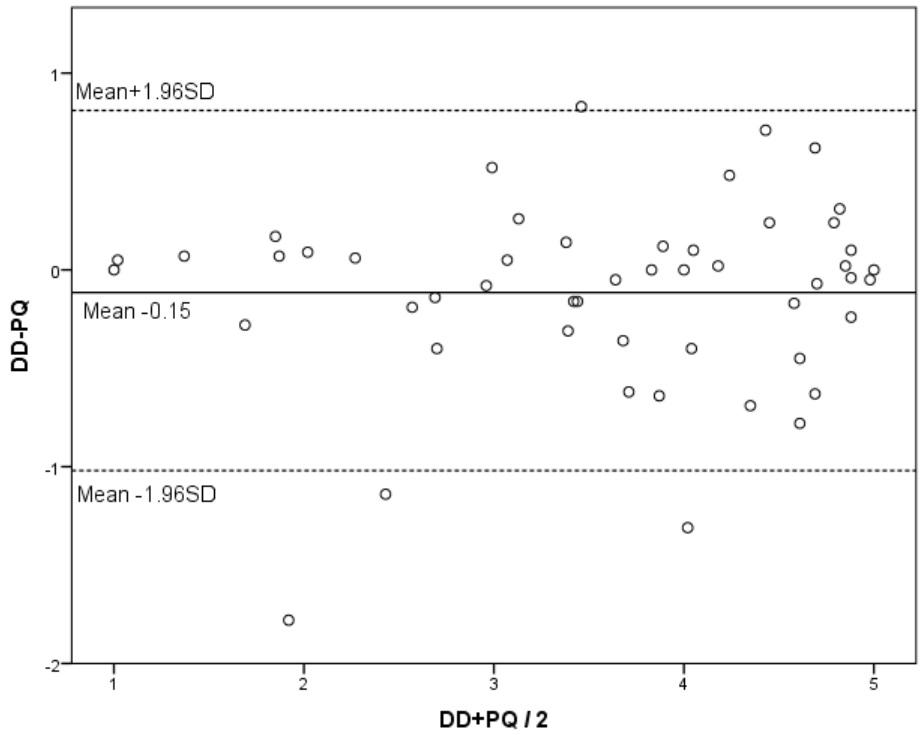
A display of the frequency distribution of scores for cooperation with the restraint for the diary versus the questionnaire is presenting similar findings indicating similar attributes were measured. The negative skew on the diary (z-score of skewness = -2.158) and on the questionnaire (z-score of skewness = -2.073) suggests both measured more participants as cooperative (see Figure 5.14). A high level of positive correlation (r_s = 0.89) was demonstrated in the scatterplot in Figure 5.15.



DD (daily diary) PQ (parent questionnaire)

Figure 5.15. Correlation between cooperation with the restraint on the daily diary and parent questionnaire.

Exploration of the limits of agreement between the scores was conducted. The cases with missing diaries (n = 5) and questionnaires (n = 9) or both (n = 3) were excluded. A total of 11 cases were excluded. The mean difference (standard deviation) of the scores was 0.15 (0.47) with the diaries tending to be scored 0.15 higher. The limits of agreement were between 0.77 and 1.07, and are shown on the Bland-Altman plot in Figure 5.16 and outlined in Table 5.3.



DD (daily diary) PQ (parent questionnaire)

Figure 5.16. Bland-Altman plot (daily diary versus parent questionnaire scores for the cooperation with restraint scores

Table 5.3. Cooperation with restraint scores on the daily diary versus parent questionnaire

Measure	n	Mean difference	SD	95% limits	Lower CI	Upper CI	Tendency
DD-PQ	51	0.15	0.47	0.129	-0.77	1.07	DD > PQ

DD (daily diary) PQ (parent questionnaire)

For cooperation with the restraint, the confidence intervals for the mean difference between the scores show that on average the daily diary could be 0.02 to 0.28 higher than the parent questionnaire.

5.5. Discussion

Fidelity to treatment includes the appraisal of a treatment intervention in terms of what was actually delivered compared to what was intended (Carroll et al., 2007). It provides a more accurate evaluation of the efficacy of a treatment and can inform the repeatability of an intervention in future studies (Bellg et al., 2004). Therefore, measures of fidelity were used in the treatment setting (i.e. home and nursery) of the CATCH trial to provide a better understanding of the intervention outcomes and to underpin repeatability in a definitive trial.

A comparison of fidelity to the CIMT across groups (measured with both data collection tools), revealed that more participants in the prolonged restraint group received a higher dose and were more cooperative. Furthermore, the scores were more consistent for both attributes in this group. A comparison of scores across groups revealed that in the prolonged restraint group the amount of therapy delivered and the child's cooperation with the restraint, was statistically significantly greater. Therefore, the novel approach to CIMT with prolonged restraint was a more effective mode of delivering therapy and more acceptable to the child, than a usual NHS CIMT approach. When this finding is related to efficacy of the CIMT interventions reported in the CATCH trial, a greater therapy delivery may underpin the reason the prolonged

restraint methodology demonstrated greater effects. Certainly, it supports previous study that more therapy provides a greater functional change (Kwakkel et al., 1999). Combining the enhanced delivery of therapy and acceptability to the child in the prolonged restraint group with greater efficacy demonstrated in the CATCH trial, suggests that further research for this novel approach to CIMT is warranted.

The high return rates of the data collection tools administered by parents /guardians (87% for the questionnaires and 94% for the diaries) evaluated in this study and administered in the CATCH trial to measure treatment fidelity suggest they were acceptable. Both had missing items although, the questionnaires tended to be more complete (dose complete on 78% of questionnaires versus 51% of diaries; cooperation complete on 80% of questionnaires compared to 45% of diaries). This may relate to the burden associated with a daily diary versus a weekly interview. Similarly the data collection tools used within the nursery setting had an 84% return rate suggesting they were acceptable, although none were complete. The return and completion rates of the measures do provide support for the acceptability of the measures and therefore, implementation in a future definitive trial.

A secondary analysis in this chapter was the association between the two different data collection tools used by parents/guardians. This was found to be high with the tools measuring similar attributes for both dose and cooperation with the restraint. The difference between the scores for individual children predominantly fell within limits of agreement of a small magnitude, demonstrating minimal variability. The mean difference revealed the scores for therapy dose measured with the

questionnaire, tended to be slightly higher than with the diary. This may be related to parents/guardians reporting error or bias the time on therapy when responding to a therapist question to present themselves in the best possible way (Macoby and Macoby, 1954). However, the agreement between techniques suggests that one method of data collection could replace the other and that perhaps only one method is required for a definitive trial. As the questionnaires were most complete this would probably be the method of choice, with adjustment made for the small systematic bias. However, fidelity measures are not only implemented to monitor interventions but also to enhance them (Bellg et al., 2004). This supports the findings by Law and King (1993) who investigated compliance to home therapeutic interventions for children with cerebral palsy. They found that completion of a daily log, by parents, was significantly correlated with the main predictor of therapy outcome (i.e., parents, self-rating of compliance).

The inclusion of measures of fidelity in the CATCH trial provided greater clarification of the delivered intervention and supported conclusions about efficacy. Nevertheless, there were limitations. The data collected was reported rather than observed therefore, has to be viewed with caution. Furthermore, there were limitations in the recording methodology. The restraint used in the novel CIMT intervention was non-removable. Therefore, therapy could have occurred outside of the structured one-to-one session and parents/guardians were not asked to record this or to differentiate between structured versus unstructured therapy. Case-Smith et al. (2012) reported a similar limitation in their study which investigated CIMT with a non-removable restraint comparing three hours with six hours of one-to-one therapy. They found no

difference in upper limb gains. However, a possible confounding factor was the non-removable restraint which meant unstructured practice could have occurred outside of the therapy time. Furthermore, the nursery data did not distinguish between missing data and non-attendance at nursery. Therefore, it was unclear what the data represented which meant that data on fidelity to treatment in the nursery setting should be viewed with caution. Measures of treatment fidelity would need to be developed for a definitive trial to allow differentiation of type of therapy and differentiation between missing data and non-attendance for nursery data collection.

There was insufficient training given to the administrators to carry out data collection primarily because of time and financial constraints. They received written instructions only and no formal face-to-face training. Consequently, the standardisation was questionable. In addition, the data collection tools were not piloted. This could have identified areas of confusion, enhanced the administrators understanding and ability to answer the questions and the fidelity measures amended before the trial (Oppenheim, 1992). Therefore, although measures of treatment fidelity are recommended for a definitive trial, further work is required on the data collection to enhance the measures including training for administrators. Pre-testing the data collection tools would be recommended before use in a definitive trial.

5.6. Conclusion

The novel approach to CIMT with prolonged restraint was a more effective mode of delivering therapy and was more acceptable to the child than usual NHS CIMT. More

therapy may underpin the reason the prolonged restraint methodology demonstrated greater effects in the CATCH trial. This supports findings from previous studies that more therapy provides greater functional change. Although, it does need to be remembered that the fidelity data was reported rather than observed therefore, some caution in interpretation required. The two data collection tools reported in this study measured similar attributes nevertheless, it is recommended that both be included in future studies, to augment treatment fidelity. However, beforehand it is advised that the reporting methodology is refined and piloting of the improved measure conducted before use in a future trial.

The enhanced treatment delivery and acceptability to the child of the prolonged restraint model demonstrated in this study in combination with greater efficacy reported in the CATCH trial, supports the case that further research into this novel approach to CIMT is warranted.

Chapter 6: A framework analysis of the parent guardian and nursery worker commentaries

6.1. Introduction

This thesis has reported on a randomised controlled trial which compared two methods of constraint induced movement therapy (CIMT) to improve functional ability in the affected upper limb in pre-school children with hemiplegic cerebral palsy (CATCH). The treatments investigated in the CATCH trial were administered primarily by the parent/guardian and nursery worker in the child's home or nursery environment. A number of studies investigating CIMT in HCP (Naylor and Bower, 2005, Eliasson et al., 2005; Smania et al., 2009; Al-Oraibi and Eliasson, 2011; Eliasson et al., 2011; Fedrizzi et al., 2012; Choudhary et al., 2013) have administered the CIMT interventions in a similar way. However, investigation of fidelity to the interventions has been minimal. Furthermore, when it has been reported such as in the study by Naylor and Bower (2005), a quantitative analysis only has been conducted, which provided a measure of intervention adherence but no understanding of the intervention administration.

It is important to understand the CIMT interventions from the perspective of the administrators because this may influence future modifications to the interventions and when fidelity is poor can highlight the need for further strategies or studies to enhance fidelity (Hoffman et al., 2014). For example, Dixon-Woods et al. (2006) conducted a qualitative examination of parental compliance to eye patching for children with a visual impairment, to provide guidance in strategies to improve

compliance rather than simply treating non-compliance as the result of information deficits (Dixon-Woods et al., 2006). Successful administration of the CIMT intervention may lead to a larger therapy dose and a greater functional change (Kwakkel et al., 1999).

A quantitative analysis of fidelity to treatment in the CATCH trial was undertaken and reported in the previous chapter. Qualitative research can be described as “interpretative research” and it can provide insights to interpret or understand quantitative research (Pope and May, 2006). The qualitative analysis presented in this chapter was employed to gain an understanding of the experiences of the parents/guardians and research workers who delivered the interventions in the CATCH trial and, the affects this may have had on administration. Therefore, the findings from the qualitative analysis were intended to provide insights into the quantitative fidelity outcomes. The aim of the study was to identify the experiences of the parent/guardian and nursery worker who were responsible for administration of the interventions for participants enrolled onto the CATCH trial and how these affect administration.

6.2. The study

The study was positioned within an interpretivist paradigm. That is, it aimed to gain an understanding as opposed to an explanation (Bryman, 2004) of the intervention administration from the perspective of the administrators. Meanings emerge from the

research process which uses naturalistic methods to construct a meaningful reality (Cohen and Crabtree, 2006).

To support clear and comprehensive reporting of the qualitative study the consolidated criteria for reporting qualitative research (Tong et al., 2007) were adhered to throughout.

6.2.1. Participants

The participants were parents/guardians and nursery workers of children recruited from June 2010 until January 2012 from 16 separate NHS community paediatric therapy services onto the CATCH trial. All the families (n = 60) who were recruited and retained on the trial were included in this study to support representation.

6.2.2. Data collection

Data was collected from two sources. The first was weekly telephone or face-to-face interviews with parents/guardians at home or in a clinic and with nursery staff, either on the telephone or at the nursery. The interviewers were qualified physiotherapists or occupational therapists responsible for conducting the CATCH trial (intervention therapist) and known to the parent/guardian and possibly the nursery worker, prior to the study commencement. The intervention therapist was inexperienced in qualitative research. They asked two questions written in a questionnaire:

“Have there been any problems this week because of the restraint or the therapy?”

“Do you have any comments?

These questions were formulated to explore parents and nursery workers perceptions of their experiences of administration of the CATCH trial in order to meet the overall aim of the study. No additional questions were asked. The administrators answered in their own words. Secondly, they answered a question in the daily diary which was in paper format and completed in the home and nursery which asked:

“Have there been any problems this week because of the restraint or the therapy?”

Again, a response was in their own words by writing either in the space provided or they used additional pages. To avoid coercion the administrators understood that they were under no obligation to respond and whether they responded or not would have no bearing on their inclusion on the trial.

6.2.3. Data analysis

The responses to the questions were written down by the intervention therapist in the questionnaire. The completed questionnaires and diaries were returned to the author of the thesis (PC) who analysed the data using framework analysis. This is an approach considered by Ritchie et al. (2007) to be systematic and includes the following stages:

- Familiarisation of the data

- Identification of recurrent and important themes to support the development of a working analytical framework
- Indexing and pilot charting
- Charting where data is summarised within the final analytical framework
- Investigation and interpretation

The analysis involved subjective choices and therefore, documentation of what had been carried out and why the choices were made were included at all stages and an audit trail available from PC. This approach was considered suitable to fit with the aims of the study and the data generated was appropriate for categorisation (i.e., was not substantially heterogeneous;Gale et al., 2013). Furthermore, not only does this approach code and index the data but also summarises it and provides a means of organising and managing the data by use of a robust and flexible matrix (Ritchie et al., 2007). The analysis was undertaken by PC who saw all the transcripts. PC was an inexperienced qualitative researcher but was aware that analysis could be influenced by the characteristics of the researcher. Therefore, she reflected throughout the research process and endeavoured to remain flexible and adaptive (Gale et al., 2013).

The familiarisation process with the content of the responses was particularly rigorous because the interviews were not conducted by PC. Following this stage, PC carefully read the responses line by line and applied open codes to describe each unit of meaning within the data. This aimed to classify the data so that it could be

compared systematically. A set of codes were developed which included an “other” code to capture any new codes and ensure data was not ignored.

The codes provided a working analytical framework which was applied to the complete data set and created a new structure for the data to support answering the research question. Subsequently this summarised data was chartered into a matrix using a spread sheet where rows represented individual cases and columns related to the codes that emerged producing cells of summarised data. This allowed analyse by case (participant) and by code (Ritchie and Lewis, 2003).

6.3. Findings

Twenty–one percent (12/58) of returned diaries included written comments and 83% (45/54) of returned questionnaires had comments recorded from parents/guardians. Furthermore four provided comments in both although, this tended to be repeat information. The detail provided and the length of the commentaries varied from one short sentence to almost two A4 pages. Of the eighteen diaries returned from the nurseries there was 89% (16/18) that included written observations. Similarly, 95% (18/19) of the nursery questionnaires included comments. Thirteen of the participants had a response provided by a nursery worker on both formats but, this tended to be replicated information. The information from the nursery environment tended to be one to two sentences per week, therefore the amount of information was more consistent than from the home environment.

Although positive changes in the upper limb were reported by parents and nursery workers the intervention was often a difficult experience for children and families. The themes identified included; the improvement of the affected upper limb, the difficulties with administration and the strategies employed to help adherence. In the quotes the following information is provided (time the quote was made, the participant's unique identifier number, the administrator and the group allocation of the participant)

6.3.1. Improvement in the affected upper limb

Parents and nursery staff from both groups commented throughout about the improvement in the use of the affected upper limb. This may have been a general remark such as "*is using affected hand more"* (week 2, 01/010, parent/guardian, manual restraint) and *"used the affected hand throughout dinner*" (week 6, 01/04 parent/guardian, prolonged restraint). At times a more detailed description of change was included. "*Getting better at grasping"* (week 4, 03/01, parent/guardian, prolonged restraint) and "will pick up biscuits, chocolate and finger foods with affected hand" (week 1, 01/015, parent/guardian, prolonged restraint). A member of nursery staff commented that the child *"was on computer using so much better"* (week 2, 12/03, nursery worker, prolonged restraint).

6.3.2. Difficulties with administration

CIMT often resulted in an emotional reaction from the child such as crying or screaming but the triggers that started the behaviour differed across groups. In the

prolonged restraint group it was often associated with the inability to carry out a task. *"He lost his temper because he found a flip phone that he could not open*" (week 6, 01/04, parent/guardian, prolonged restraint) and *"feels frustrated at not being able to play puzzles"* (week 1, 14/04, parent/guardian, prolonged restraint). A similar finding was described at nursery, *"couldn't do messy play so became cross and upset*" (week 2, 13/02, nursery worker, prolonged restraint). Some children in the prolonged restraint group did settle down and became less distressed. "*Crying to take it off for the first few days"* (week 1, 01/013, parent/guardian, prolonged restraint) and *"initial distress at restraint but lasted less than 2 hours*" (week 1, 01/011, parent/guardian, prolonged restraint).

Conversely, the poor behaviour in the manual restraint group tended to be because the unaffected upper limb was held to provide the manual restraint. *"Upset when trying to restrain the hand, he cried as soon as it was touched"* (week 1 to week 6, 01/014, parent/guardian, manual restraint). *"He resists the restraint, and pulls away"* (week 5, 03003, parent/guardian, manual restraint), *"screamed and had a temper tantrum when had hand restrained"* (week 1, 04/03, parent/guardian, manual restraint). A similar picture was described at nursery. *"I tried when eating but (he) did not accept the restraint"* (week 2, 01/010, nursery worker, manual restraint). Furthermore, the accounts suggested that these children did not tend to settle but the behaviour became worse over time. *"Is more resistant and gets frustrated"* (week 3, 03/03, parent/guardian manual restraint) and "*became more headstrong.....more difficult to get her to do the therapy"* (week 3, 03/03, parent/guardian, manual restraint).

Another problem with CIMT (prolonged restraint only) was related to a limitation in the child being unable to carry on as usual. One parents revealed that *"Washing is really difficult; she is used to do more for herself*" (week 1; 13/03, parent/guardian, prolonged restraint). Another child who was usually mobile was described as *"frightened to come down the stairs on his own due to balance"* (week 1, 01/015, parent guardian, prolonged restraint). Likewise, at times usual routines were disrupted*, "not been able to bath him or give him a bread stick in the car"* (week 1, 11/02, parent/guardian, prolonged restraint). Additionally, usual sleep patterns were interrupted *"a couple of nights of upset, as couldn't put dummy back in"* (week 1, 13/02, parent/guardian, prolonged restraint), and another described that their child *"found it hard to get comfortable at night and settle to sleep"* (week 4, 01/04, parent/guardian, prolonged restraint).

Nursery workers described a similar impact for some children on their usual participation in nursery life. *"Unable to access messy play and swimming*" (week 2, 13/002, nursery worker, prolonged restraint) and *"he found it hard to eat and join in with his friends"* (week 1, 07/04, nursery worker, prolonged restraint). One nursery portrayed three separate scenarios affected by the CIMT. *"Needed a little more help with toileting"* (week 1*....."Struggles at tea time with sandwiches"* (week 2)..... *"Found difficulty playing on the climbing frame as could not hold on*" (week 4, 14/002, nursery worker, prolonged restraint).

The occurrence of accidents posed another problem for CIMT with prolonged restraint. *"Had a very bad slip while trying to catch himself by restricted hand, it slipped and he fell knocking his head on shelf quite a bad bruise* (week 6, 01/04, parent guardian, prolonged restraint). Another parent/guardian "*had to remove cast at around 6:30 pm as it got wet…….. Fingers very smelly and wrist very red and wrinkly and swollen due to damp"*. (week 1, 01/09, parent guardian, prolonged restraint). Furthermore, on removal of the cast a parent/guardian described *"there was not only redness due the splint being damp but also bruises made by the splint*". (week 1, 01/07, parent guardian, prolonged restraint).

Accounts suggested that administrators for both CIMT methodologies found it burdensome. *"Thought it was going to be really easy to get 60 minutes of treatment in, difficult as his younger sister takes quite a lot of time up"* (week 1, 01/02, parent/guardian, manual restraint). Another commented that they *"found it difficult to do exercises as four other children. …….Dad tries to do when he comes home from work"* (week 1-week 3, 04/01, parent/guardian, manual restraint). Additionally, a parent/guardian remarked that *"they were unable to carry out programme because of work commitment*" (week 5, 01/016, parent/guardian, manual restraint). An additional comment was *"It is too many weeks*" (week 6, 12/003, parent /guardian, prolonged restraint). The nursery staff made comments about the impact the interventions had on nursery life with reference to staffing levels. *"Difficult with staffing in class*" (week 1 -week 2, 01/06 nursery worker, prolonged restraint).Another stated that "fits in quite well because of (good) staffing levels and timetable" (week 2, 13/02 nursery worker, prolonged restraint) and "*staff off sick not able to do so often*" (week 5, 3/02 nursery

worker, manual restraint). However, there were some positive comments from the parents /guardians applying the prolonged restraint methodology. "*Easy to incorporate into the day. little bits at a time"* (week 3, 10/02 parent/guardian, prolonged restraint) and "*quite easy to do especially if you do over mealtimes*" (week 6, 13/02, parent/guardian, prolonged restraint).

6.3.3. Strategies employed by the administrators

Despite the difficulties encountered some families and nursery workers went to substantial efforts to encourage adherence to the interventions. For example, one parent/guardian *"removed the bandage everyday while G asleep*," (week1, 01/011, parent/guardian, prolonged restraint) in an effort to make the intervention more comfortable. Another parent stated that *"felt he was bored therefore encouraged him to help in the kitchen, wiping up etc*" (week 3, 01/015, parent/guardian, prolonged restraint). Additionally, if a task proved to be difficult *"objected when feeding*", equipment was provided "*managing a lot better since using chunky cutlery*" (week 2, 03/01 parent/guardian, prolonged restraint). A similar approach was described by a nursery worker "*did not want to feed herself.....nursery has brought some angled spoons"* (week 1, 02/01, nursery worker, prolonged restraint) and another *"provided him with a straw*" (week 3, 14/02, nursery, prolonged restraint).In a similar way in the manual restraint group adherence was enhanced by adapting the intervention structure. "*Leave her to play for a while then come back later to try restraint again, so do not force her"* (week 2, 03/02, parent/guardian, manual restraint) and "worked in 20 minute blocks" (week 4–week 5, 05/01, parent/guardian, manual restraint). In

addition, the strategy employed to deal with protestation to the physical holding was to discontinue. "*Sometimes just verbally encouraged without having to manually restrain"* (week 3, 01/02, parent /guardian, manual restraint) and "*the staff discontinue activity when (she) resists so she doesn't get upse*t" (week 2, 03/02, nursery worker, manual restraint).

6.4. Discussion

The qualitative analysis has provided insights into the experiences of the parents/guardians and research workers who delivered the interventions in the CATCH trial and the effects on administration. Parents/guardians gave consent for their child to partake in the trial and then found themselves responsible for the application of the intervention in the home. If they persevered it may have led to a number of negative outcomes. The child may find using the affected upper limb clumsy and unsuccessful leading to a difficult, stressful situation, there may have been minor adverse events and limitation to usual participation. Both CIMT methodologies potentially led to distress and could be time consuming for the administrators who were often busy people. Despite this parents/guardians went along with the interventions and a number of accounts suggested considerable effort were made to enhance adherence. It may be that the negative outcomes are acceptable to parents/guardians so long as there is some indication that the intervention was valid. Descriptions of improvement of the affected upper limb provided by parents/guardians would suggest that maybe they relied on this improvement for validation and this provided justification to continue.

This supports previous work exploring parents' experiences of administration of occlusion (patching) for treatment of amblyopia. Dixon-Woods et al. (2006) described parents who found it a difficult role to fulfil often because of the distress and tensions it caused. Parents were described as highly sensitive to the intervention credibility which they based on demonstrable improvement in vision. If no improvement could be detected it was likely that treatment was abandoned. Indeed, the relationship between improvement and parental compliance was such that they concluded compliance to the patching may in part be a marker of a treatable amblyopia.

The emotional reactions of the children to the CIMT intervention may also have an effect on the quality and frequency of the intervention delivery. This may subsequently affect the willingness of the parents to comply. Law and King (1993) found parental compliance with therapeutic interventions in children with cerebral palsy was affected by a number of factors. Among them was how skilful parents felt at delivering the intervention and if they were able to fulfil the prescribed frequency and duration. However, the emotional reaction to the CIMT described may have impacted on the quality, frequency and duration of the interventions delivered. The poor quality and reduced delivery may reduce parental compliance. Although some training on the intervention administration was given it was not provided on managing the emotional reaction of the child to the CIMT interventions. Therefore, to enhance the delivery of future interventions and parental compliance to the interventions, extending training to include behaviour modification training would be advised.

The strategies employed by the administrators to deal with the resulting poor child behaviour may in part be reflected in the difference in the amount of therapy delivered across groups. In the manual restraint group administrators reported that they discontinued in response to the child's behaviour. In the prolonged restraint group however, there was much less option to discontinue with the restraint. Therefore, the more permanent nature of the restraint may have meant if the child objected the administrator was more likely to choose a different strategy, such as provision of equipment to make the task easier. This may result in the child being more successful at the task and more accepting of the intervention. This finding may provide some understanding about the quantitative outcome on fidelity to treatment across groups, outlined in the previous chapter with more therapy delivered in the prolonged restraint group. CIMT is a complex intervention (i.e., contains several interacting components; Medical Research Council, 2006). Therefore, it is important to understand which of those components may impact on the success of the intervention. This is especially in terms of therapy dosage in light of the work conducted by Kwakkel et al.(1999) that found more therapy can lead to a greater functional change. Furthermore, the commentaries did describe a number of different strategies included by parents/guardians and nursery workers such as the provision of equipment already described and the option of constraint removal at night for comfort. These require further testing to possibly incorporate into a definitive trial.

The study does have a number of limitations. The CATCH trial recruited from a large area however, the characteristics of the parents/guardians and nursery workers was not collected therefore, it was not clear how diverse they were and therefore, how

representative. The researcher PC coded the data but, to offer an alternative viewpoint it is recommended that this should be carried out by more than one person (Gale et al., 2013). It was considered that the patient, public involvement representative (JM) be approached however, this was not feasible but recommended in future research. The data relied on accounts of child behaviour rather than direct observation therefore, could be biased. In addition, data collection was conducted by the intervention therapist who was known to the parents/guardians and responsible for the trial and could be the child's NHS therapist. Therefore, this relationship may have affected the responses. Therapists' independent from the study and the family would be recommended to collect data for future studies. Contemporaneous research notes were used to collect the data however, in a definitive trial a recommendation that audio equipment be used and transcripts returned to the administrators for comments and corrections, to provide a more accurate reflection of the administrators views (Tong et al., 2007). Furthermore, if resources had allowed other qualitative research methods (observation studies, in-depth interviewing and focus groups) would have been used in the CATCH trial to access different levels of knowledge and provide a wider understanding (Pope and Mays, 1995). Further research using different methodologies would be recommended for future research.

6.5. Conclusion

This study has highlighted that administration of the CIMT interventions investigated in the CATCH trial can lead to difficult, stressful and time consuming experiences for the administrators. Despite the many difficulties encountered, they often persevered

and justification to continue may be provided by improvement of the affected upper limb, which validated the interventions. Furthermore, a number of administrators employed strategies which aimed to enhance fidelity, which require further investigation. The permanent nature of the prolonged restraint meant when the child was poorly behaved the administrators tended to continue and distract the child whereas in the manual restraint group the trend was to stop. Although the study is limited because the analysis was conducted by one researcher only and data was recorded using contemporaneous research notes on reported rather than observed data, it may provide some understanding about the larger quantitative treatment delivery in the prolonged restraint group. It is recommended that future studies be conducted using other qualitative methodologies, to access different levels of understanding. Understanding the CIMT interventions from the perspective of the administrators is important especially in light of the work conducted by Kwakkel et al.(1999) that found more therapy can lead to a greater functional change.

Chapter 7: Development and validation of the Birmingham Bimanual Questionnaire administered in the CATCH trial.

7.1. Introduction

The Birmingham Bimanual Questionnaire (BBMQ) is a parent-reported questionnaire. It was developed for the randomised controlled trial to compare two methods of constraint induced movement therapy (CIMT) to improve functional ability in the affected upper limb in pre-school children with hemiplegic cerebral palsy (CATCH trial), reported in this thesis. It evaluates bimanual function in children with a unilateral motor impairment from the perspective of the parent/guardian and can be administered as a face-to-face interview, or self-administered. Parental self-reported opinion had the potential to provide knowledge about the users own perceptions of the intervention outcomes. This was considered important and recommended by an international group of expert clinicians to be included in the measures of CIMT effectiveness in future research (Eliasson et al., 2013).

A face-to-face interview was planned for the CATCH trial, however, there was a reduction in resource allocation for the follow-up assessments during the trial following expansion of recruitment nationally and a self-administered questionnaire was proposed. A substantial amendment to the protocol was made (AMO1 16/12/2010; see Appendix 1). The primary outcome measured with the Assisting Hand Assessment (AHA; Krumlinde-Sundholm et al., 2007; Krumlinde-Sundholme and Eliasson, 2003) was not developed as a self-administered assessment.

Therefore, an electronic search of the literature was carried out to find a suitable parent-reported postal questionnaire. Three were identified; Abilhand-Kids (Arnould et al., 2004); Paediatric evaluation of disability inventory (PEDI; Haley et al., 1992); Paediatric Movement Assessment Log (PMAL; Taub et al., 2004), however, none were suitable. The Abilhand-Kids assessment was considered unsuitable based on age range, the PEDI was developed for children presenting with motor delay rather than unilateral impairment and the PMAL required further validation (Wallen et al., 2009).

This chapter will report on the development and psychometric validation of the BBMQ a parent-reported tool to measure assisting hand function of the affected upper limb in pre-school children with HCP. Initially the processes undertaken in the development and content validation will be described. The psychometric analysis undertaken on the BBMQ will be then be outlined including; face validation, criterion validation, construct validity, floor and ceiling effects, internal consistency reliability and a case-by-case agreement. The results of the development and evaluation of the BBMQ will be presented along with a discussion of the findings.

7.2 Methods

7.2.1 Development and content validation of the BBMQ

The AHA was the primary outcome measure in the CATCH trial. Its purpose was to measure and describe how effectively children with unilateral disabilities such as

HCP used their affected hand when performing bimanual activities. The development of the AHA was based on the identification of observable actions required for bimanual hand skills. Subsequently, these actions were constructed into items to measure the ability of the upper limb and evaluated by Krumlinde-Sundholme and Eliasson (2003). They found that good representation of bimanual hand skill was provided by the items. Furthermore, adequate reliability and validity of the AHA has been demonstrated (Holmefur et al., 2009). The AHA is now well established and frequently used in clinical practice (Krumlinde-Sundholm, 2012). A script of the AHA can be found in Appendix 6.

To ensure the BBMQ included items which represented bimanual skills, its construction was based on the content of the AHA, which consists of 22 items, clustered into six categories. The six categories are: general usage (3 items); arm use items (4 items); grasp and release (7 items); fine motor adjustment (3 items); coordination (2 items); and pace (3 items). To check the content validity of the BBMQ, each item was cross referenced with the AHA categories and is outlined in Table 7.1.

Table 7.1. Cross-reference of BBMQ items with AHA categories.

BBMQ items	AHA categories (number of items)					
	General Usage (3)	Arm use (4)	Grasp /Release (7)	Fine motor (3)	Co (2)	Pace (3)
Using their affected arm and hand to keep objects still to play with.	**X**					
Using the affected arm and hand for big movements that use the whole arm e.g. reaching, waving or leaning on it.		**X**				
Grasping an object with their affected hand			**X**			
Releasing an object with their affected hand.			**X**			
Moving the fingers of the affected hand				**X**		
Using both hands together					**X**	

Birmingham Bimanual Questionnaire (BBMQ) Assisting hand Assessment (AHA)
Coordination (Co)

The BBMQ was developed to be self-administered and therefore, content validation also needed to consider the readability by parents/guardians. To examine readability, a reading ease formula (Flesch, 1948) was administered (i.e., the Flesch-Kincaid Reading Test). Scores range between 0 and 100 and a higher score indicated easier readability.

7.2.2. Validation of the BBMQ

The results from the CATCH trial (see Chapter 4) were used to assess the validity of the BBMQ. This primarily included the response rates and scores from the BBMQ, and scores from the AHA. However, the scores from the bimanual hand function rating from QUEST were also employed in this validation study.

7.2.2.1. BBMQ

The BBMQ asked parents/guardians to rate the difficulty their child had had in completing six upper limb tasks with their affected upper limb over the previous month. The BBMQ tool is shown in Figure 7.1. As the tool does not require that tasks be observed during testing, no specific equipment was required. It was estimated to take ten minutes to complete. The tasks rated included; keeping objects still to play with, big movements that use the whole arm, grasp, release, moving the fingers and use of both hands together. The parents/guardians were able to answer with one of five responses numerically coded which were; never = 0, almost never = 1, sometimes = 2, often = 3, and almost always = 4. None of the items were weighted. A total mean score was calculated, and a lower magnitude score indicated less difficulty and therefore better bimanual hand function.

Birmingham Bimanual Questionnaire (BBMQ)
We would like to know the difficulties your child has with their affected arm and hand. That is the arm/hand that they do not use so well.
Please tell us how difficult each one of the items below has been for your child during the past ONE month by circling 0-4:
There is no right or wrong answer.
If you do not understand a question, please ask for help

Difficulty with…..…	Never	Almost never	Some times	Often	Almost always
Using their affected arm and hand to keep objects still to play with.	0	1	2	3	4
Using the affected arm and hand for big movements that use the whole arm e.g. reaching, waving or leaning on it.	0	1	2	3	4
Grasping an object with their affected hand	0	1	2	3	4
Releasing an object with their affected hand.	0	1	2	3	4
Moving the fingers of the affected hand	0	1	2	3	4
Using both hands together	0	1	2	3	4

Figure 7.1. Birmingham Bimanual Questionnaire.

7.2.2.2 Data analysis

Response rates of the BBMQ and the quantity of data completion were reported as percentages. For ease of comparison between the BBMQ and AHA scores, the individual scores on the BBMQ were categorised as follows; 0 = 100%, 1 = 75%, 2 = 50%, 3 = 25%, and 4 = 0%. This allowed both tools to have a scoring system which changed in the same direction (i.e., a higher score represented better function) and used the same scale (0-100). Histograms were constructed of the BBMQ and AHA scores and z-scores of skewness were calculated. Scatter plots were constructed to assess the relationship between the scores from each tool. Spearman's correlation coefficients were computed (due to the non-normal distribution of the data; Field, 2009), to quantify the relationship between the BBMQ-AHA and BBMQ-QUEST scores. All statistical analysis was conducted using IBM SPSS version 20.

7.2.2.3 Psychometric analyses

Face validity relates to whether a scale looks reasonable and appears relevant (Streiner and Norman, 2008). Parents may object to completing irrelevant questions therefore, the return rates and the quality of data completion were referenced to examine face validity of the BBMQ.

A measurement tool such as the BBMQ developed to measure an aspect of health, needs to ensure that it measures the full range of that health status (Terwee et al., 2007). If it does not, it can be limited in reflecting change. According to Mchornay and

Tarlov (1995) more than 15% of participants achieving either the lowest or highest score indicates the presence of floor and/or ceiling effects. The BBMQ scores were examined and the proportion that scored either the lowest or highest was calculated.

The criterion validity of the BBMQ was examined against the reference standard (Terwee et al., 2007). Construct validation of the BBMQ was evaluated by comparing the BBMQ scores with the pre-defined bimanual hand function rating on QUEST. The effect sizes of the correlation coefficients were interpreted using Cohen (1988) rule of thumb, i.e., a “small” effect size is .20, a “medium” effect size is .50, and a “large” effect size is .80.

A new measurement tool such as the BBMQ may be expected to correlate well with a tool developed to measure the same underlying construct (Bland and Altman, 1986), such as the AHA. Therefore, further exploration of the relationship between the BBMQ and the AHA scores was required. A case-by-case comparison, using the Bland and Altman (1986) method was made between the BBMQ and AHA scores. This method plots the difference between BBMQ and AHA scores for individuals against the average of both scores. It reveals if a systematic bias or variance between the scores is present. Furthermore, it can identify possible outliers. However, the interpretation of bias and variance between the scores is based on clinical implications (Bland and Altman 1986).

To assess the extent individual items of the BBMQ are consistent with each other and to reflect a singular construct, the internal consistency reliability of the BBMQ

was examined (Field, 2009). The 24-week data was utilised because it was administered only by parents/guardians whereas a therapist had been available at the other time points. Initially, correlation between individual items of the BBMQ with the overall score was explored. A correlation of <.3 was unacceptable (Field, 2009). An overall Cronbach's alpha (α) coefficient (Cronbach, 1951) was calculated and an α-coefficient of >.6 was considered to be an appropriate level to support internal consistency reliability (Cronbach, 1951). Furthermore, the α-coefficient was examined following the deletion of individual items.

A summary of the analyses performed as part of the validation of the BBMQ is provided in Table 7.2.

Table 7.2. Summary of psychometric analyses of the BBMQ.

Analysis performed	Description
Face validity	Face validity relates to whether a scale looks reasonable and appears relevant (Streiner and Norman, 2008). BBMQ return rates (percentages) were referenced to evaluate face validity.
Floor and Ceiling effects	Percentage of lowest/highest scores calculated, >15% indicates floor and/or ceiling effects (Mc.Horney and Tarlov, 1995)
Criterion validity	Criterion validation i.e., the extent a new tool relates to a "gold" or reference standard (Terwee et al., 2007).Scatter plots and frequency distributions between the BBMQ and AHA scores were observed and quantified using z-scores of skewness (scores <1.96 indicated that the distribution was normal). Spearman's correlation coefficients were computed to quantify the relationship between the tools. The effect sizes of the correlation coefficients were interpreted using a rule of thumb developed by Cohen (1988) i.e., a "small" effect size is .20, a "medium" effect size is .50, and a "large" effect size is .80.
Construct validity	Construct validation refers to whether a measurement tool has expected relationships with relevant variables (Bland and Altman, 2002) and can be assessed by testing specific, predefined hypotheses (Terwee et al., 2007). The BBMQ scores were expected to demonstrate good correlation with the bimanual hand function rating from QUEST.
Agreement	Exploration of the agreement between case-by-case BBMQ and AHA scores were provided using a Bland and Altman (1986) method. This allowed any systematic bias and variance between scores to be established and outliers identified.
Internal consistency reliability	Internal consistency reliability explores the extent individual items of a tool are consistent with each other and reflect a singular construct (Field, 2009). Correlation between items and total scores were computed (<.3 indicates no correlation). Cronbach's alpha (α) coefficient was calculated for the BBMQ scores at 24-weeks (.>.6 demonstrates an appropriate level) (Cronbach, 1951). Additionally, reliability was explored following item deletion.

7.3. Results

7.3.1. Content validation

Mapping items to the categories of the AHA supports content validation of the BBMQ in terms of coverage of the key bimanual hand skills. All categories had at least one representative question in the BBMQ other than the pace category, which had none and the grasp/release category which had two representative questions.

The BBMQ achieved a readability rating of 71.3 and was classified as fairly easy to read and suitable for children aged 11 to 13 years (Scott, 2013). However, the BBMQ was modified following feedback from a parent/guardian and version 2 was developed. The term “affected upper limb” became “affected hand and arm. That is the hand and arm that they do not use so well”. Furthermore, the format of the responses was changed from a list to a table. Following modification, the BBMQ (version 2) was re-assessed with the Flesch-Kincaid Reading Test and the rating slightly improved to 73.9.

7.3.2. Face validity

In terms of the return rate of the BBMQ questionnaires, 81% (50/62) were returned by the parents/guardians at baseline. Eight did not complete a questionnaire because their baseline assessments were administered before the BBMQ was introduced to the CATCH trial. Four parents/guardians completed version one of the BBMQ, which

were excluded. Ninety seven percent (60/62) of the BBMQs at the ten-week assessment and, 95% (59/62) at 24-week assessment were returned. None of the questionnaires had missing data. The return rates and quality of data support the face validity of the BBMQ and its relevance to the parents/guardians.

7.3.3. Floor and Ceiling effects

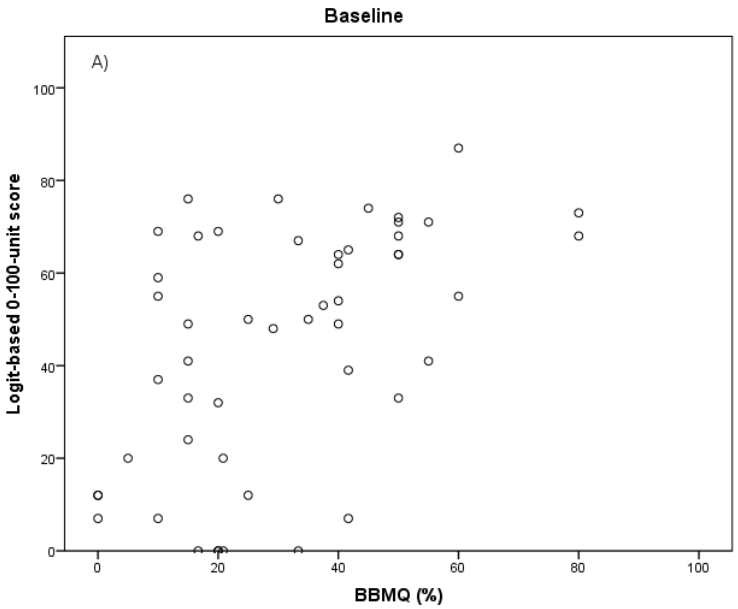
The proportion of parents/guardians who scored either the highest or the lowest value on the BBMQ was calculated. The lowest value was scored by 4% (2/50) at baseline, 5% (3/60) at the ten-week assessment, and 3% (2/59) at the 24-week assessment. No participants scored the highest value. Given that findings were lower than the recommended 15% value (Mc.Horney and Tarlov, 1995) floor or ceiling effects were not demonstrated in the BBMQ.

7.3.4. Criterion validation

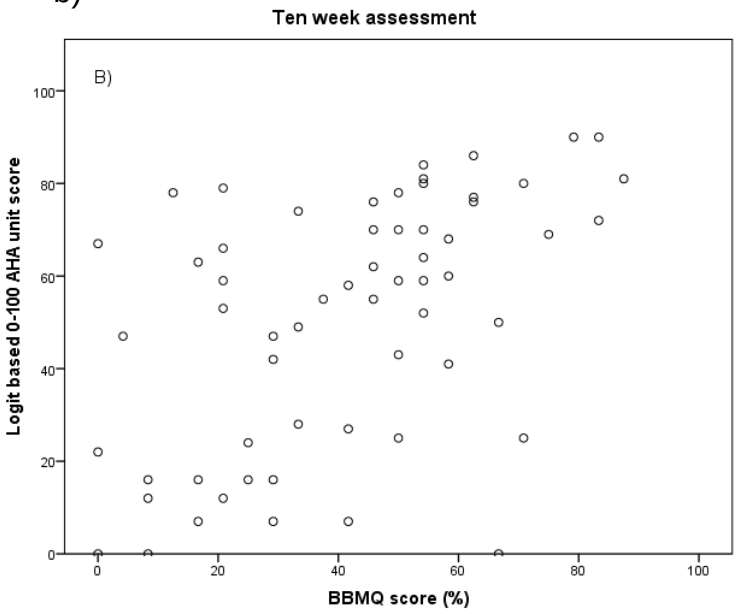
Frequency distributions of the BBMQ and AHA scores were constructed. The z-scores of skewness at baseline for the BBMQ and AHA were 1.42 and -1.19 respectively which suggests that the tools may measure different attributes. At the ten-week assessment, the z-scores of skewness for the BBMQ were -.0.10 and 1.53 for the AHA indicating again that different characteristics were assessed.

Scatter plots for the baseline and ten week BBMQ and AHA scores (Figure 7.2.a) and Figure 7.2.b) showed a positive association.

a)



b)



Birmingham Bimanual Questionnaire (BBMQ) Assisting hand Assessment (AHA)
Figure 7.2. Scatter plots of the BBMQ and AHA total scores at a) baseline and b) ten-week assessment

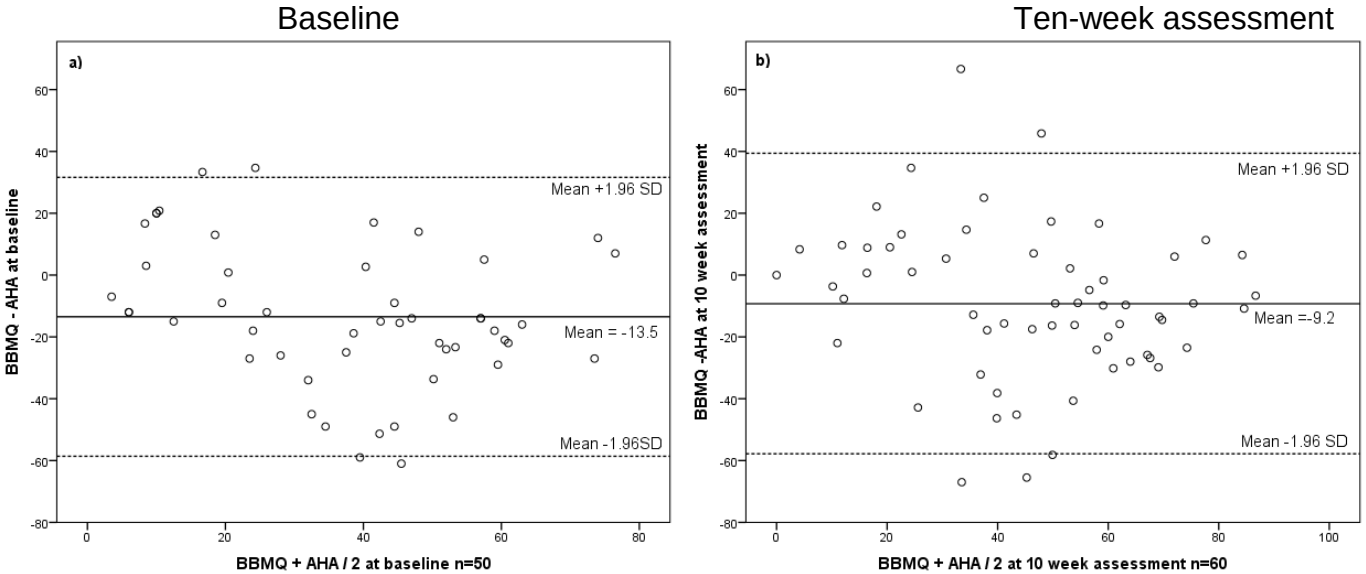
Spearman's correlation coefficient was r_s = .474 at baseline (blinded data) and r_s = .523 at the ten-week assessment (non-blinded data) both were statistically significant ($p < .001$) indicating a medium relationship (Cohen, 1988).

7.3.5. Construct Validity

A subjective rating of the child's bimanual hand function using a scale of (0 to 10; poor = 0 to good = 10) from QUEST was made by the assessor (PC) for each child at baseline and the 10-week assessment. Spearman's correlation coefficient was used to evaluate the correlation between the subjective rating and the BBMQ scores. At baseline r_s = .46 and at the ten-week assessment r_s = .460. The values suggest a medium correlation.

7.3.6. Agreement

A case-by-case comparison was made between the BBMQ and AHA scores at baseline (blinded data) and at the ten-week assessment (non-blinded data). The results are outlined in Table 7.3. A graphical representation is provided in the Bland-Altman plots (Figure 7.3.a) and 7.3.b). The AHA systematically predicted better bimanual hand function by 9.2 (baseline), and 13.5 (ten-week assessment), which was a relatively small amount (total score for both scales was 100). However, there was a large variability between the scores and the limits of agreement at both assessment time points was > 45. Additionally, there were a number of outliers (i.e., three at baseline and four at the ten-week assessment).



Birmingham Bimanual Questionnaire (BBMQ) Assisting hand Assessment (AHA)

Figure 7.3. A Bland-Altman plot showing the agreement between BBMQ and AHA scores for individual children at a) baseline and b) ten-week assessment.

Table 7.3. Agreement between AHA and BBMQ scores for individual children at baseline and ten-week assessment

Assessment time point	Measure	n	Mean difference	SD	95% Limits	95% CI (lower)	95% CI (Upper)	Tendency
Baseline	BBMQ-AHA	50	-13.5	23.0	45.1	-58.6	31.6	AHA predicts higher
Ten-weeks	BBMQ-AHA	60	-9.2	24.8	48.6	-57.8	39.4	AHA predicts higher

7.3.7. Internal consistency

Cronbach's α-coefficient for the BBMQ scores at the 24-week assessment time point was .891 and suggests a strong internal consistency reliability (>0.6 indicates an acceptable level for measures of physical attributes such as the BBMQ (Cronbach, 1951).

Table 7.4. Correlation between BBMQ individual items and total scores

BBMQ items	Correlation between each item and total score
1.Keeping objects still	0.607
2.Using affected upper limb for big movements	0.571
3.Grasping an object	0.641
4.Releasing an object	0.813
5.Moving the fingers	0.528
6.Using both hands together	0.775

The correlation between the BBMQ individual items and total scores was examined and shown in Table 7.4. The item which correlated best with the total score was releasing an object (.813) and the least correlation was with moving the fingers item (.528).

Table 7.5. Cronbach's (α) alpha coefficient for BBMQ items. (BBMQ score for six items was .891)

Item deletion of the BBMQ	Cronbach's (α) alpha coefficient if item removed
1.Keeping objects still	0.885
2.Using affected upper limb for big movements	0.889
3.Grasping an object	0.880
4.Releasing an object	0.858
5.Moving the fingers	0.896
6.Using both hands together	0.865

The internal consistency reliability was .891 when examined with all items present. However, individual items were deleted and the tool re-examined. The results ranged from .858 when the item "releasing an object" was deleted to .896 when the "moving the fingers" item was removed (see Table 7.5). Internal consistency reliability was improved only following the removal of the item "moving the fingers" by .005 to .896.

7.4. Discussion

Construction of the BBMQ was based on the AHA which aims to measure bimanual performance in children with unilateral disabilities. The AHA has evidence of adequate validity and reliability (Holmefur et al., 2009; Krumlinde-Sundholm et al., 2007). Subsequent mapping of the items from the BBMQ against the AHA categories indicated that the key concepts relevant to bimanual hand skills are included in the BBMQ which supports its content validation. The pace category was not represented

in the BBMQ, because the items relate to motivation and cognition (AHA Manual). It was thought that these terms are difficult to comprehend for lay members of the public (i.e., parents/guardians). The single grasp/release category in the AHA had two representative questions (grasp and release) in the BBMQ. This was because they are assessed as separate entities in clinical practice. Furthermore, the grasp/release category had substantially more items than other AHA categories. Therefore, two questions in the BBMQ made a greater contribution to the total score. Streiner and Norman (2008) recommended that a self-assessment questionnaire should be appropriate for people with a reading age of up to 12 years. This was fulfilled by the BBMQ which was classified as suitable for 11-13 year olds.

The very high response rates and quality of completion of the BBMQ are consistent with a tool that appears to be relevant and demonstrates face validity (Streiner and Norman, 2008). The tool does not require specific equipment and can be completed in approximately ten minutes and so poses minimal administrative or participant burden.

A medium correlation between the BBMQ and AHA total scores was found. This suggests that both tools measured a similar construct and given that the AHA is the reference standard provides some support for criterion validation of the BBMQ. The aim of the BBMQ is for parents/guardians to estimate their child's bimanual ability using a rating scale. The BBMQ was compared with an evaluation by the assessor (PC) using a rating scale of bimanual function on QUEST at baseline and ten-weeks.

A comparison between the scores and the BBMQ at the same time points revealed a moderate correlation. This offers support to construct validity of the BBMQ.

The internal consistency of the BBMQ was found to be high. This suggests that the BBMQ could discriminate between children based on their bimanual hand skills. However, the internal consistency reliability improved following removal of the item “moving the fingers”. This item may be a poor fit to the bimanual hand function model because of the presence of involuntary finger movements or unintentional mirror movement. These are defined as, involuntary movements of one side of the body (mainly upper limb) and can be seen in children with hemiplegic cerebral palsy (Gallea et al., 2011). The BBMQ item “moving the fingers” does not differentiate between involuntary and purposeful movement. Therefore, unintentional finger movements which have no association with bimanual hand skill may have been inadvertently scored. It is recommended that for future use this item be removed from the BBMQ.

The comparison of the case-by-case scores for the BBMQ and AHA using a Bland-Altman (1986) plot demonstrated a large variability between the scores, which suggests poor agreement. This indicates that the BBMQ should not replace the AHA in clinical practice. However, the BBMQ could complement the AHA allowing a quantitative assessment from the parents/guardians. The BBMQ and AHA were both developed to measure bimanual skills. However, the lack of case-by-case agreement could reflect the differences in a number of aspects of the tools. The BBMQ is a short (six items) tool administered by an untrained parent/guardian in contrast to the AHA a

22 item measure conducted by a specialist therapist. Furthermore, the therapist had undergone three days of training to become a validated AHA scorer. The diversity of methods of capturing data between the BBMQ and the AHA may have led to variability. The former asked parents/guardians to evaluate activity retrospectively from the previous month, whereas in the AHA the therapist scored activity based on a video clip from a recorded play session. The data from parents/guardians may have been affected by recall bias whereas in the recorded play session the child may have been reluctant to comply. Both factors may affect outcome and potentially lead to variability between tools.

An exploratory analysis was conducted on the scores on the Bland-Altman plot (1986) that fell outside the 95% limits (i.e., three at baseline and four at the ten-week assessment). Of the seven cases, four of them (i.e., 57%) had an ethnicity of Non-white British. This suggests that future administration of the BBMQ may require additional support if English is not the first language.

Although this evaluation has provided substantial support for the validation of the BBMQ there were limitations. It would have been more appropriate to develop and evaluate the BBMQ before the CATCH trial rather than after the trial had commenced. A number of participants were not evaluated at baseline with the BBMQ because it had not been developed or version one used and those participants excluded. Furthermore, pre-testing with a small number of respondents should have been conducted. This would have highlighted areas of confusion, checked the

parent/guardians understanding and ability to answer the questions and made amendments before rather than after the study start (Oppenheim, 1992).

Ideally, the BBMQ should have been assessed for test-retest reliability to identify any random error (Field, 2009). This would be conducted by a repeat of the BBMQ by the same parent/guardian on two occasions, separated by an interval of time. Sufficient time would need to have elapsed to account for recall bias but not so much that the child's motor skills could have matured and the bimanual hand skill changed (Bland and Altman, 2002). A lower time limit of one to two weeks is judged often to be appropriate (Terwee et al., 2007). In the context of the CATCH trial it was considered a substantial burden to administer a second self-assessment for a parent/guardian. Given these considerations, test-retest reliability was omitted. However, it is considered to be a priority for a future study to provide an evaluation of random error.

The outcomes from the BBMQ assessments need to be approached with some caution because the parents/guardians were aware of group allocation. Therefore, the BBMQ were non-blinded assessments and their subjective nature meant the outcomes could be open to distortion (Sedgwick, 2011). However, given the age of the participants and requirements for consent it was not possible to administer a parent-reported outcome by blinded assessors. Assessment of parental self-reported opinion using the BBMQ informed the CATCH trial about the users own perceptions which was considered by a consensus of expert clinicians on CIMT as important and a priority for future research (Eliasson et al., 2013). Given the knowledge gained

using the BBMQ it would be recommended (following further validation and piloting) in a definitive trial.

7.5. Conclusion

This study provided evidence which supports the use of the BBMQ as a parent-reported tool to measure bimanual hand skills of the affected upper limb in pre-school children with a unilateral disability. Its ease of use may provide a way to inform on the users own perceptions about treatment effectiveness. Some caution is required however, because of the assessor's awareness of group allocation. The BBMQ should not replace the AHA, but instead be used as a complementary measurement tool.

Chapter 8: Systematic review and meta-analysis of constraint-induced movement therapy in the treatment of the upper limb in pre-school children with hemiplegic cerebral palsy

8.1. Background

Constraint induced movement therapy (CIMT) has been developed as an upper limb intervention for children with hemiplegic cerebral palsy (HCP) see Section 1.5 for an overview. This thesis has reported on a randomised controlled trial to evaluate two methods of CIMT to improve upper limb function for pre-school children with HCP (CATCH). A novel model of CIMT whose development was guided by application within an NHS environment was compared to a usual NHS CIMT. The development of the novel CIMT was influenced by a Cochrane systematic review (Hoare et al., 2007) which is critiqued in Section 1.5. Subsequently, there have been a number of clinical trials conducted in the HCP population to evaluate CIMT (Sakzewski et al., 2014). However, the Cochrane systematic review conducted by Hoare et al. (2007) has not been updated and includes a wider age range than the CATCH trial.

The aim of this systematic review and meta-analysis was to evaluate the effectiveness of CIMT implemented in a manner compatible with the intervention protocol of the CATCH trial in pre-school children. Relevant trials from the existing Cochrane systematic review conducted by Hoare et al. (2007) are included and searches were updated for any new relevant controlled studies. This review however, is confined to studies which investigated CIMT in pre-school children with HCP.

8.2. Methods

The search strategy of studies, assessment of risk of bias and reporting of results was conducted in line with the Preferred Reporting Items for Systematic Reviews and meta-analysis (PRISMA) statement (Liberati et al., 2009). The item checklist from PRISMA was adhered to for reporting the review and a copy is included in Appendix 9.

8.2.1. Eligibility criteria

8.2.1.1. Participants

Studies that evaluated children with a diagnosis of HCP due to a congenital or acquired insult with any degree of motor disability, or co-morbidities (other than those which led to progressive motor deficit) were included. However, only those which evaluated pre-school children (up to 60 months). If study participants were older children, the study was included only if the majority were 60 months or less. A lower age limit for the review was not specified. However, it was expected that most participants would be 12 months or more because the diagnosis of cerebral palsy (CP) is often delayed as it is based on an emerging clinical presentation (Rosenbaum, 2006).

8.2.1.2. Intervention

The CIMT model used in the CATCH trial administered a prolonged (non-removable short wrist cat/splint) method of restraint to the unaffected upper limb for six weeks duration. The therapy consisted of intensive practice (one hour each day) and was administered primarily by parents/guardians and nursery workers. A therapist offered advice and guidance each week. Studies were included in the review only if the intervention combined the two key components (restraint of the unaffected upper limb and intensive training of the affected upper limb) as originally described by Taub et al. (1993). Different models of the intervention have been described in the literature. This includes a number of techniques of restraint (e.g., removable mitt, a removable arm sling, a long arm wrist cast and manual holding). The review included studies that investigated CIMT using different restraint techniques other than manual holding because this was the comparator in the CATCH trial. All combinations of frequency and duration of CIMT interventions were included. Furthermore, a variety of administrators (i.e., parents or therapists), treatment environments such as a clinic or at home and dosage have been described. Studies were not excluded based on administrators or intervention environment.

The expected change in the affected upper limb may be based on motor learning theory and this approach is usually administered by occupational or physiotherapists. Alternatively, the intervention may be underpinned by a behavioural approach called shaping (i.e., tasks are divided into small, manageable steps and verbal reinforcement provided (Taub, 2004). This method has been predominantly offered by psychologists. Whichever was described, the study was included.

Studies have described treatment adjuncts which have been administered with the CIMT. For example, Case-Smith et al. (2012) described a hybrid CIMT in which an episode of bimanual training was included either concurrently or immediately afterwards. Furthermore, other studies have described adjuncts such as drug therapy or electrical stimulation. The CATCH trial protocol was developed for suitability within an NHS environment and did not include adjuncts. Therefore, studies which described CIMT with adjuncts were excluded from the review.

8.2.1.3. Outcome measures

The outcome measures included were those compatible with the measures used in the CATCH trial and administered at a similar time point. Motor activity (i.e. carrying out a task) can be categorised into usual (performance) or best available (capacity; International Classification of Functioning, Disability and Health; ICF; World Health Organisation, 2001). The CATCH trial included assessment of performance (Assisting Hand Assessment, AHA; Krumlinde-Sundholm and Eliasson, 2003; Krumlinde-Sundholm et al., 2007) and capacity (Quality of Upper Extremity Skills Test; QUEST; Dematteo et al., 1992) immediately post-intervention. The review included studies which administered performance and capacity assessment immediately post-intervention. Furthermore, in line with the CATCH trial, health related quality of life and parent-reported outcome measures were included immediately post-intervention and at follow-up.

8.2.1.4. Type of studies

Included studies had a control group that received either conventional therapy or no treatment whether randomised or not. Cross-over trials, where participants receive the intervention from each group and act as their own controls but the sequence is randomised, were included, however data from the first treatment phase from this study design only were included. This was to deal with the possible risk of bias due to the carry-over effects of CIMT into the second treatment phase (Higgins and Green, 2011). Studies randomised at a cluster level such as per centre were also included. Studies which used human participants only have been included. Full papers, conference abstracts and theses have been included as were papers not written in English.

8.2.2. Search strategy

The systematic review and meta-analysis was conducted using a protocol based on the recommendations from the Cochrane Collaboration and PRISMA statements (Liberati et al., 2009). A search strategy to identify relevant articles was conducted using the same search strategy employed by the Cochrane systematic reviewers (Hoare et al., 2007) and commenced from the endpoint date of their search. The databases were initially searched in November 2013 and alerts set up to capture any new studies and a final update conducted in December 2014. They included the Cochrane Central Register of Controlled Trials (CENTRAL; The Cochrane Library 2006, Issue 3), MEDLINE (2006- December 2014), EMBASE (2006-December 2014), CINAHL (2006-December 2014) and Psych Info (2006-December 2014). In

addition, reference lists of articles and conference abstracts were examined. An example search strategy conducted in MEDLINE with no language restrictions was applied and is outlined in Figure 8.1.

MEDLINE (Ovid)

1. Constraint adj3 therapy.tw
2. CIMT.tw
3. CI therapy.tw
4. Forced.tw
5. Massed practice.tw
6. or/1-5
7. Cerebral palsy
8. Cerebral pals$.tw
9. Hemiplegia/
10. Hemiplegi$.tw
11. or/7-10
12. 6 and 11

Figure 8.1. An example search strategy

8.2.2.1. Data collection

The titles and abstracts of the search results were downloaded onto Endnote x5 software. Duplications were removed and citations were screened for inclusion. Those that failed the inclusion criteria were removed. The remaining studies were retrieved and reviewed in full text by the author (PC) to determine if they met the inclusion criteria. If the decision about inclusion was questionable, the study was referred to another reviewer (CC) who discussed it with the author (PC). The checklist for data extraction from the Cochrane Handbook for Systematic Reviews of Interventions (Version 5.1.0; Higgins and Green, 2011) was used to extract the relevant data. This was conducted primarily by the author (PC) with guidance from another reviewer (CC) and is outlined in Appendix 9.

8.2.3. Quality assessment

The included studies were quality assessed, guided by an adaption of the quality assessment tool for assessing risk of bias administered in the Cochrane systematic review (Hoare et al., 2007). The tool included an assessment of the randomisation process, allocation concealment, blinding and loss to follow-up and the following grades were used: A (adequate), U (unclear), I (inadequate) NA (not-applicable). Criteria for grading are outlined in Table 8.1

Table 8.1. Quality assessment tool.

Level of methodological quality	Adequate (A)	Unclear (U)	Inadequate (I)
Adequacy of randomisation process	Satisfactory sequence generation reported using computer random number generator, random number tables.	Did not specify one of the adequate reported methods in (A) but a randomisation method mentioned.	Other methods of allocation that appear to be unbiased.
Adequacy of allocation concealment process	Passable measures to conceal allocations.	Unclearly concealed trials. Concealment not reported or not credible	Inadequately concealed trials. Method of allocation was not concealed.
Attrition bias	An intention-to-treat analysis was possible. Few losses to follow up noted.	Exclusions reported but were<10%.	No reporting on exclusions, or > 10% or wide differences in exclusions between groups
Level of blinding	Assessor adequately blinded Treatment provider and participant cannot be blinded.	Uncertainty about blinding of the assessor.	The assessor was inadequately blinded.

(Adapted from Hoare et al., 2007)

8.2.4. Data analysis

The preferred method for handling continuous data was adhered to and is outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Version 5.1.0; Higgins and Green 2011). Where appropriate results from individual studies have been pooled quantitatively by meta-analysis and plotted in forest plots. If different scales were administered to measure the same attribute a standardised mean difference was computed. This requires the same type of score (final value or mean change from baseline) across studies to be combined (Higgins and Green, 2011). Preference was given to mean change scores from baseline rather than comparing final value or means (SD) at specific time points. This was in line with the reported outcome in the CATCH trial. In some circumstances it can be more powerful to compare mean change from baseline than final values as it removes a component of between-person variability (Higgins and Green, 2011). This was considered appropriate because of the heterogeneity of the HCP population and relatively small sample sizes. If mean change scores were unavailable for the primary outcome the corresponding authors were contacted to obtain data. If it was unavailable final value mean (SD) scores were used.

The standardised mean differences (i.e., effect sizes) have been interpreted as: 0.2 a small effect 0.5 a moderate effect and 0.8 a large effect (Cohen, 1988). Random effect modelling was adopted as a method of addressing both within

and between group variance for the studies included in the meta-analysis. The meta-analysis was conducted using Review manager (Rev Man) version 5.2.

8.2.4.1. Assessment of heterogeneity

Mean and standard deviation data plotted in forest plots were assessed visually. Furthermore, the amount of inconsistency in the results of the included studies, not due to chance was calculated as I2 and expressed as a percentage. Heterogeneity of 0% to 40% was considered unimportant, 30% to 60% as moderate, 50% to 90% as substantial and 75% to 100% considerable (Higgins and Green 2011).

8.3. Results

8.3.1. Study selection

A total of 745 citations were identified and downloaded onto Endnote x5 software. Duplicates were removed and 427 titles and abstracts remained. These were screened by the author (PC) and 214 removed. Two hundred and thirteen titles and abstracts remained. Following examination of either the abstracts or full texts against the pre-determined inclusion conditions a further 207 studies were excluded. A flow chart of study identification, screening, eligibility, inclusion and reasons for exclusion is shown in Figure 8.2. Thirty five (two from the Cochrane systematic review) clinically controlled trials investigating CIMT in the CP population were excluded. A list of these excluded clinically controlled trials and reasons for exclusion are shown in Appendix 9.

Six studies from the search were included in the review and combined with a study (Eliasson et al., 2005) from the existing Cochrane systematic review (Hoare et al., 2007) and the CATCH trial (see Figure 8.2). Therefore eight studies were included in the review.

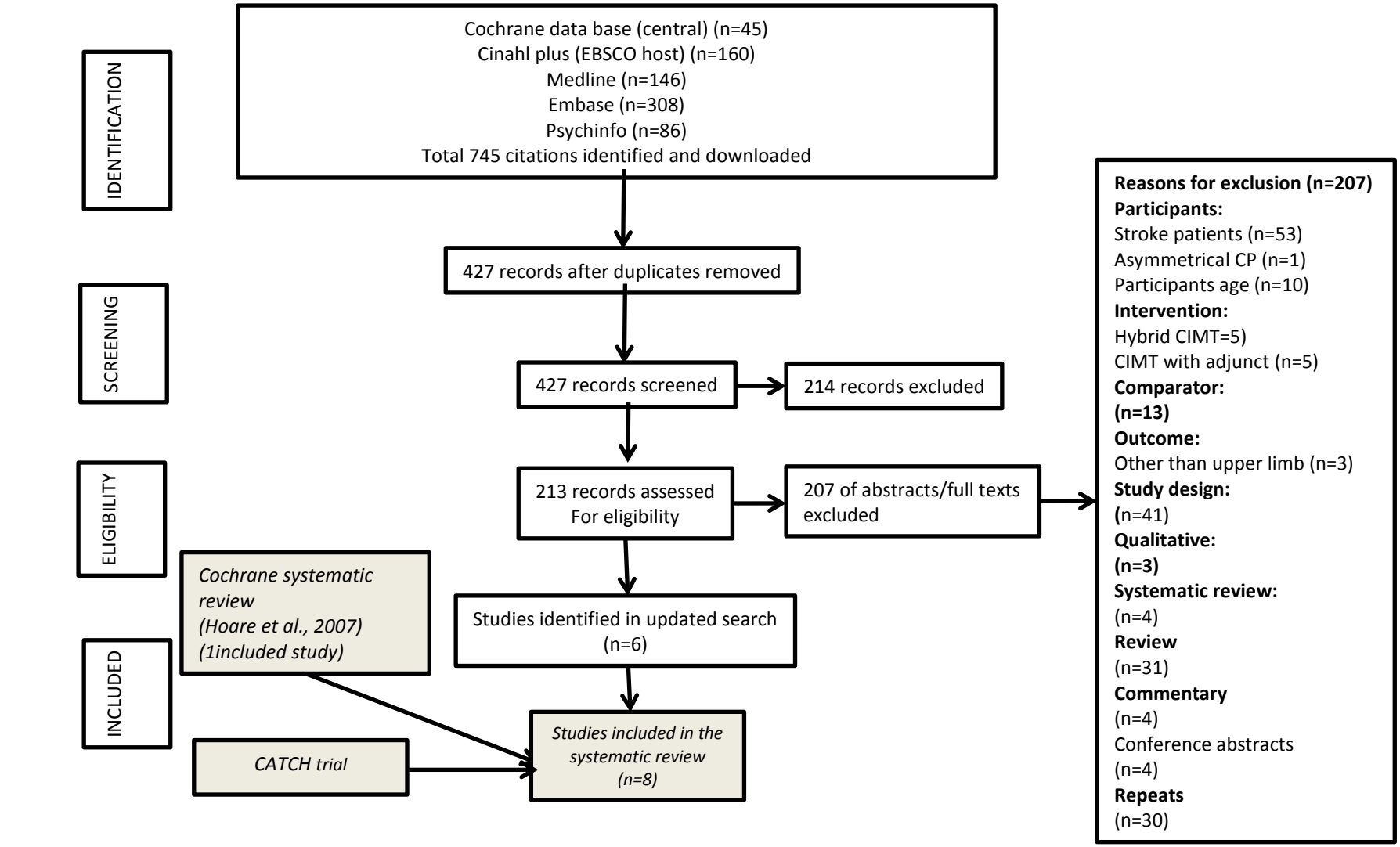


Figure 8.2. Flow chart of systematic review and meta-analysis

8.3.2. Included studies

There were eight studies included (Choudhary et al., 2013; Al-Oraibi and Eliasson 2011; Fedrizzi et al., 2012; Eliasson et al., 2011; Smania et al., 2009; Abootalebi et al., 2010; Eliasson et al., 2005; and the CATCH trial). Four of the studies were parallel group randomised controlled trials (RCTs; Choudhary et al., 2013; Al-Oraibi and Eliasson, 2011; Abootalebi et al., 2010; CATCH trial). There was one cluster RCT (Fedrizzi et al., 2012) and two cross-over RCTs (Eliasson et al., 2011; Smania et al., 2009). A clinical controlled trial (CCT) conducted by Eliasson and colleagues (2005) was included. In total, the trials recruited 262 participants. A list of the included studies, their design and size are included in Table 8.3.

Table 8.2. Descriptors of included studies

Study	Study design	n
Choudhary et al., 2013	RCT	31
Al-Oraibi and Eliasson, 2011	RCT	14
Fedrizzi et al., 2012	Cluster RCT	69
Eliasson et al., 2011	Cross-over RCT	25
Smania et al., 2009	Cross-over RCT	11
Abootalebi et al., 2010	RCT	12
Eliasson et al., 2005	CCT	41
CATCH trial	RCT	60

8.3.3. Study descriptors

Data was extracted from each included study using a data extraction tool (Higgins and Green, 2011) and the results are shown in Appendix 9. A descriptive summary for each included study (except the CATCH trial) is provided below.

Choudhary et al., (2013) conducted an RCT (n = 31) with a mean (SD) age of 58.5 (17.7) months (CIMT) and 62.7 (18.0) (Control). Children were excluded if they had mild motor symptoms of their affected upper limb (difference in QUEST between upper limbs of <10%) or excessive spasticity (≥ 3 on the Ashworth scale). In addition, children had to understand simple commands, be able to sit without support and have good vision. Included children were randomised to receive either two hours per day of CIMT, over a four week period or conventional therapy. The CIMT was delivered by either an occupational therapist (OT) (30%) or parent (70%) and restraint of the unaffected upper limb, accomplished by a sling. The protocol included a total of 66 hours of CIMT. The Quality of Upper Extremity Skills Test (QUEST; (DeMatteo et al., 1992) was administered immediately post-intervention (four weeks) to measure effectiveness.

Al-Oraibi and Eliasson (2011) conducted an RCT with 14 participants who had a mean (SD) age of 56.6 (24) months. Although children with all motor presentations were included, they had to be of normal intelligence with a family who were likely to cooperate with the intervention. The participants were randomised to receive either two hours per day of CIMT over an eight week period or conventional therapy. The

CIMT was primarily administered by parents/nursery workers (86%) or an OT (14%). The unaffected upper limb was restrained with a wrist splint. One hundred and twelve hours of CIMT was included in the protocol. The outcome of the intervention was measured immediately post-intervention (eight weeks), with the Assisting Hand Assessment (AHA; Krumlinde-Sundholm and Eliasson, 2003; Krumlinde-Sundholm et al., 2007)

The cluster RCT (Fedrizzi et al., 2012) which included 69 children aged between two and eight years. All degrees of motor disability of the affected upper limb and developmental abilities were included. Participants were randomised to receive one of three interventions (CIMT, bimanual training or usual therapy). CIMT or usual therapy only, was included in this systematic review. Either three hours per day, of CIMT, over a ten week period or usual therapy, was administered. The CIMT was delivered by either a parent (79%) or an OT (21%). Restraint of the unaffected upper limb was accomplished by a wrist splint. A total of 210 hours of CIMT was included in the protocol. Two outcome assessments (QUEST and the BESTA scale) were administered immediately post-intervention (ten weeks), to evaluate effectiveness.

Eliasson et al. (2011) performed a cross-over RCT with 25 children who had a mean age of 26.1 months (range:20-32) in the CIMT group and 31.2 months (range:24-39) in the control group. Although no restrictions in terms of motor ability of the affected upper limb were made, the children included in the study had to be able to cooperate with the testing procedure. All participants received both CIMT and the control

intervention but the sequence was randomised. The CIMT intervention involved two hours per day of CIMT, for an eight week period. The CIMT was delivered predominantly by a parent/ pre-school worker (93%), or an OT (7%). A wrist-splint was applied to restrain the unaffected upper limb. A total of 112 hours of CIMT was delivered and its effectiveness assessed using the AHA, immediately post-intervention (eight weeks).

In a cross-over RCT conducted by Smania et al. (2009), eleven participants with a mean (SD) age 57 (24) months were randomised to a sequence in which they first received either CIMT or usual intervention. Only children with a mild to moderate motor disability of the affected upper limb were included. In addition, they had to have good physical health and the ability to participate in the proposed activities. The children were randomised to receive either eight hours per day of CIMT over a five week period or conventional therapy. The CIMT was delivered primarily by parents (95%) or an OT (5%) and restraint of the unaffected upper limb accomplished by a wrist-splint. A total of 200 hours of CIMT was included and the effectiveness immediately post-intervention (five weeks) measured, using the Use test and Function test, which were trial specific assessment tools.

An RCT was conducted by Abootalebi et al. (2010) which included 12 children with a mean (SD) age 59.9 (9.15) months. They were only included if they could grasp an object and had >10 degrees of wrist and finger extension on the affected upper limb. Furthermore, they had to be able to participate in activities and excluded if they had hearing or visual problems. Included children were randomised to receive either five

hours per day of CIMT for three weeks or conventional therapy. The CIMT was delivered only by an OT. A sling was used to restrain the unaffected upper limb and a total of 105 hours of CIMT was included. The Peabody developmental motor scale (PDMS) post-intervention (three weeks) was administered to measure effectiveness.

One study, (Eliasson et al., 2005) from the Cochrane systematic review (Hoare et al., 2007) met our inclusion criteria. Forty-one children with a mean (SD) age of 28.8 (8.2) months (CIMT) and 30.8 (10.9) months (Control) were evaluated. Participants with any degree of motor disability of the affected upper limb were included. However, they were excluded if they were unable to understand simple commands or if there was nobody to deliver the intervention at home. Group allocation was based on postcode (i.e., children who lived in Stockholm (where the rehabilitation centre was located) were included in the CIMT group the control group was recruited from elsewhere. Children either received two hours per day of CIMT over an eight week period or conventional therapy. Primarily the CIMT was administered by a parent or nursery worker (93%) or an OT (7%). A wrist splint was used to restrain the unaffected upper limb. A total of 112 hours of CIMT was delivered and measured post-intervention (eight weeks) with the AHA.

8.3.4. Risk of bias of included studies

The included studies were described in terms of the criteria listed in the methodological quality assessment tool adapted from Hoare et al. (2007) shown in Table 8.1. Baseline characteristics were also described. A grade was given for each

criteria and a summary of the assigned criteria grades per study is shown in Table 8.4.

Table 8.3. The criteria grades per study.

Study	Randomisation	Allocation concealment	Follow-up	Blinding
Choudhray et al. (2013)	A	A	A	U
Al-Oraibi and Eliasson (2011)	U	I	I	U
Fedrizzi et al. (2012)	U	U	A	U
Eliasson et al. (2011)	A	A	I	A
Smania et al. (2009)	U	U	A	A
Abootalebi et al. (2010)	U	A	A	U
Eliasson et al. (2005)	NA	NA	A	A
CATCH trial	A	A	A	A

A (adequate), U (unclear), I (inadequate), NA (not-applicable).

8.3.4.1. Baseline participant characteristics

All trials recruited children with a diagnosis of HCP with the majority of participants aged up to 60 months. However, studies included different exclusion criteria which potentially meant participants differed. Upper limb motor disability of any severity was included other than in Choudhary et al. (2013), Smania et al. (2009) and Abootalebi et al. (2010). The exclusion criteria meant only children with mild to moderate upper limb motor disability were included. Studies also excluded children based on other

developmental presentations, including the inability to sit independently (Choudhary et al., 2013), delayed intellectual ability (Al-Oraibi and Eliasson, 2011) and non-cooperation with the intervention by the participant and family (Eliasson et al., 2005; Eliasson et al., 2011; Al-Oraibi and Eliasson, 2011). In addition, children were excluded based on the presence of co-morbidities including: severe behavioural problems (Smania et al., 2009); visual and hearing problems (Abootalebi et al., 2010) and; uncontrolled epilepsy (Choudhary et al., 2013). Furthermore, exclusion of children was based on recent interventions including botulinum toxin injections to the upper limb (Fedrizzi et al., 2012)

Baseline characteristics were reported and compared across groups in all studies with the exception of two (Smania et al., 2009; Abootalebi et al., 2010). The RCT conducted by Choudhary et al. (2013) reported no differences on age, comorbidities, and upper limb function between the CIMT and the control group. Similarly, the trial (Al-Oraibi and Eliasson, 2011; CIMT reported no difference across groups on age ($p = .25$) or hand function ($p = .20$). The participants in the study by Fedrizzi et al. (2012) were found to have no differences on age ($p = .24$), severity of upper limb impairment ($p = .60$) or cognitive level ($p = .07$) at baseline. Although the trial conducted by Eliasson et al. (2011) reported no difference on age ($p = .45$), and perceived development ($p = .24$) despite randomisation they did report a statistically significant difference in severity of hand function ($p = .017$) across groups. The clinical controlled trial by Eliasson et al. (2005) matched children on age and severity of hand function and reported no statistically significant differences. The CATCH trial reported no difference across groups at baseline (see Chapter 4.3).

8.3.4.2. Randomisation and adequacy of allocation concealment

To protect group assignment before randomisation, two studies (apart from the CATCH trial) utilised a computer to generate an unpredictable group allocation sequence (Choudhary et al., 2013; Eliasson et al., 2011). The study by Abootalebi et al. (2010) described a procedure where the participant's names were written on a piece of paper and drawn out of a hat. The randomisation procedure for all remaining studies was unclear. Fedrizzi et al. (2012) only made reference to randomisation being conducted at centre level. Al-Oraibi and Eliasson (2011) merely specified the personnel involved (i.e., the first author and a study coordinator). Smania et al. (2009) failed to provide any detail about randomisation and allocation concealment. The study carried out by Eliasson et al. (2005) did not conduct a randomisation procedure for group allocation. Instead, children living locally to the treatment centre (metropolitan Stockholm) were invited to participate in the intervention group. The control group were recruited from other areas where paediatric programmes were conducted.

8.3.4.3. Blinding

The intrinsic nature of the CIMT protocol meant that the parents/guardians and nursery workers or the intervention therapists could not be blinded to the intervention. However, every study described a blinding procedure of the assessor with the exception of Abootalebi et al. (2010) although of varying degrees. For instance three studies (Eliasson et al., 2005; Eliasson et al., 2011; Al-Oraibi and Eliasson, 2011) separated the AHA (a tool developed to be scored from a videotape) into

administration and scoring procedures. Eliasson et al. (2011) used a blinded assessor to administer the AHA and maintained blinding by ensuring they were not involved in the interventions. The scoring was conducted, by a different therapist using a videotape which had no personal data attached. Although Eliasson et al. (2005) did not use a randomisation procedure for group allocation, they blinded the assessor who was also not involved in the intervention or data collection. However, in the study conducted by Al-Oraibi and Eliasson (2011), it was unclear if any therapists were blinded. The videos were scored by a therapist unaware of the study aims. The CATCH trial blinded the assessor to group allocation and put a number of measures in place to maintain blinding (outlined in Chapter 3.10).

The study by Smania et al. (2009) did not specify whether the therapists who conducted the assessments were blinded. However, the assessments were videoed and the tapes scored by an examiner unaware of group allocation and study aims. Despite using assessments that have been developed for face-to-face administration (i.e., QUEST), the study by Fedrizzi et al. (2012) scored the assessments from videos but did not specify, if the assessors were blinded. The videos were quality assessed, but it was not specified how this was done. Conversely, Choudhary et al. (2013) described blinding the therapists who taught the therapy to the parents/guardians as well as the assessor who had no involvement with the interventions. However, they did not describe measures to ensure continued blinding. Given that the assessment (QUEST) required direct contact with the participant there was a risk of group disclosure.

8.3.4.4. Intention to treat and attrition bias

Intention to treat analysis relates to the study outcome irrespective of whether or not the participant followed the treatment stipulated in the protocol. A number of studies reported minimal immediate post-intervention drop-outs including: a three percent (1/31) of participants in the Choudhary et al. (2013) study, and three percent from the CATCH trial (2/62), four percent (3/72) in the Fedrizzi et al. (2012) trial. Eliasson et al. (2005) reported slightly more dropouts at eight percent (4/45) and Smania et al. (2009) recorded nine percent (1/11). However, two studies reported high drop-outs which may have led to attrition bias. Al-Oraibi and Eliasson (2011) reported thirty percent (6/20) dropout but did not specify group allocation and Eliasson et al. (2011) reported 24% (8/33) with six participants missing from the CIMT group.

8.3.5. Effect of the intervention

8.3.5.1. Activity performance measures

Five studies including the CATCH trial measured bimanual motor performance following CIMT versus usual practice immediately post-intervention. Four studies administered the AHA (one with the AHA logit unit and three with the logit-based 0-100 AHA-unit). Another study used the BESTA bimanual sub-score. The scores were combined using a standardised mean difference (SMD) because different scales were administered and final value scores were utilised in this synthesis (mean change was not available for all studies). No summary effect (SMD 0.02: 95% CI: -0.35, 0.38) of CIMT was demonstrated. The variation in the observed estimates between studies was quantified using I^2 and found to be 38% and considered moderate (Higgins and Green, 2011). The effect estimates from each study and the overall summary effect is illustrated in the forest plot in Figure 8.3.

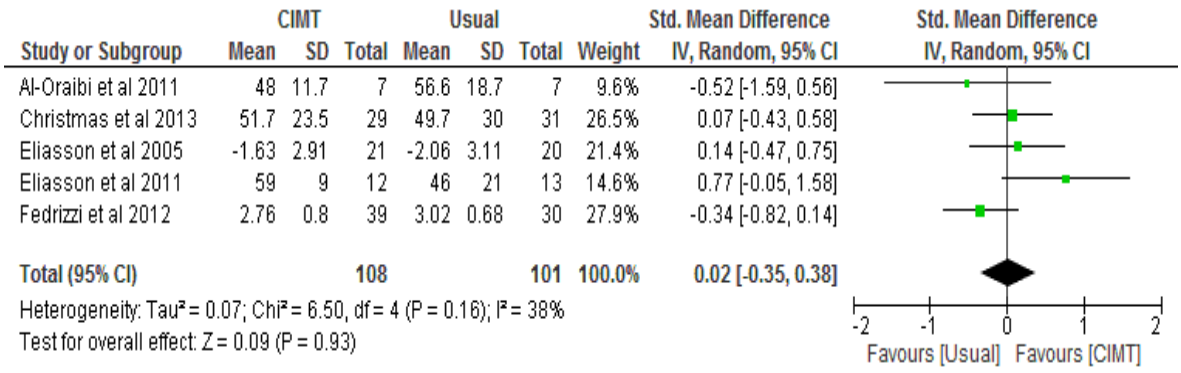


Figure 8.3. Meta-analysis combining the activity (performance) outcomes (final value scores) immediately post-intervention.

A difference in mean change AHA scores across groups from baseline was reported in the CATCH trial and the meta-analysis aimed to combine these findings with the same findings from other studies. The mean change scores were available only for Eliasson et al. (2005) reported in a Cochrane systematic review (Hoare et al., 2007). In order to obtain the standard deviation of the mean difference authors (Eliasson, 2011; Al-Oriabi et al., 2011) were contacted by email. No replies were received and therefore, not included. The mean difference across groups of the AHA logit scale was reported. It has a range of -10.26 to 8.72 logits and the smallest detectable difference (0.97 logits; Krumlinde-Sundholm, 2012). The effect estimates from each study and the overall summary effect is illustrated in the forest plot in Figure 8.4. When combined, a statistically significant treatment effect was demonstrated in the CIMT group (MD 0.92,95% CI: 0.46, 1.38) equivalent to the smallest detectable difference. Variation in the observed estimates between studies, not due to chance, was quantified using I^2 and found to be 0%.

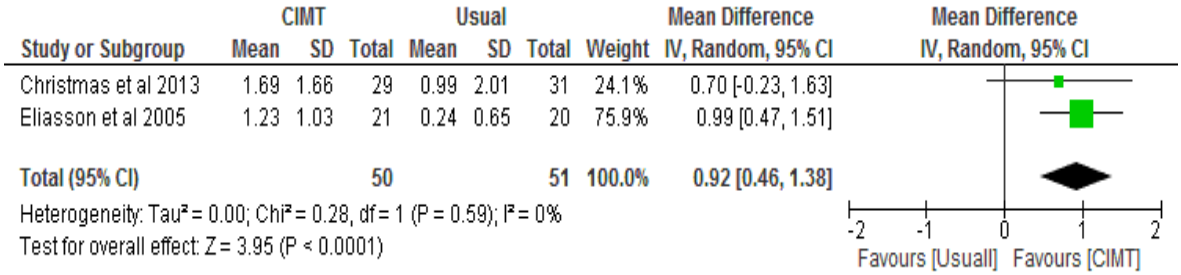


Figure 8.4. Meta-analysis combining the AHA (logit scale) mean change scores from baseline to immediately post-intervention

8.3.5.2. Activity capacity measures

QUEST is a measure of motor capacity and was administered in three studies (Choudhary et al., 2013; Fedrizzi et al., 2012; the CATCH trial). It consists of a total score and four domain scores (grasp, dissociated movement, weight-bearing and protective extension. Each study administered the same scale therefore, a mean difference (MD) (using final value scores) in QUEST total scores across groups was computed. QUEST has a percentage score with a smallest detectable difference of 13.8% (Klingels et al., 2008) . The summary effect (MD 1.84, 95% CI: -2.30, 5.99) favoured CIMT but not significantly and was considerably smaller than the smallest detectable difference. It is illustrated in the forest plot shown in Figure 8.5 with the effect estimates from each study. Variation in the observed estimates between studies was quantified and the I^2 = 14% represents a minimal heterogeneity (Higgins and Green, 2011).

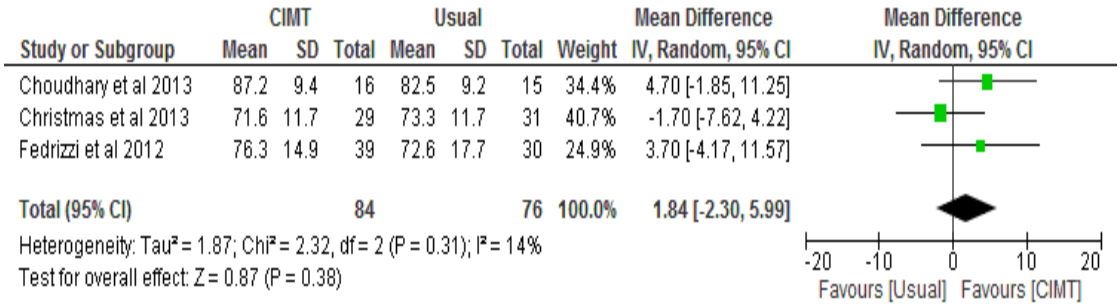


Figure 8.5. Meta-analysis of QUEST total final value scores immediately post-intervention

Domain scores were pooled when available (Fedrizzi et al., 2012; reported for the grasp domain score only). Final value scores were combined and mean difference (MD) calculated on the QUEST grasp sub-score from three studies (Choudhary et al.,

2013; Fedrizzi et al., 2012; CATCH trial). The effect estimates from each study and the overall summary effect (MD 3.26, 95% CI: -3.19, 9.71), which favoured CIMT but not statistically significantly is illustrated in the forest plot in Figure 8.6. Variation in the observed estimates between studies, not due to chance, was quantified (I^2 = 48%), suggesting moderate heterogeneity (Higgins and Green, 2011).

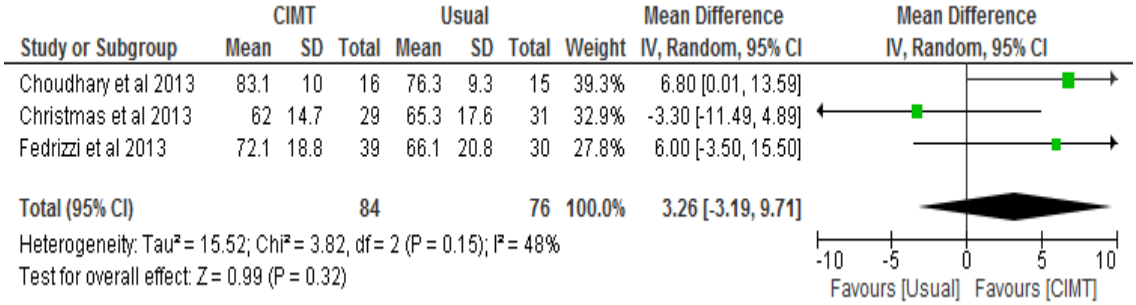


Figure 8.6. Meta-analysis of QUEST final value grasp domain scores immediately post-intervention.

Final value scores from the study by Choudhary et al. (2013) were combined with the CATCH trial for the three remaining domain scores (dissociated movement; weight bearing; and protective extension).

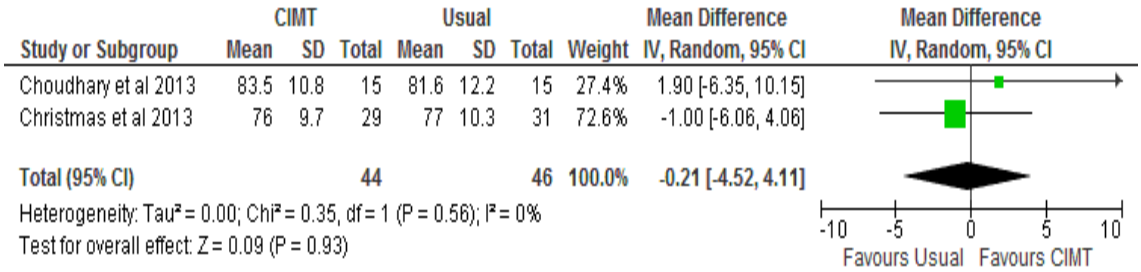


Figure 8.7. Meta-analysis of QUEST dissociated movement final value domain scores immediately post-intervention

Effect estimates for the dissociated movement domain score are illustrated in the forest plot in Figure 8.7. Overall, usual practice was slightly favoured (MD -0.21, 95%

CI: -4.52, 4.11). Heterogeneity between studies was quantified (I^2 = 0%) and therefore, minimal.

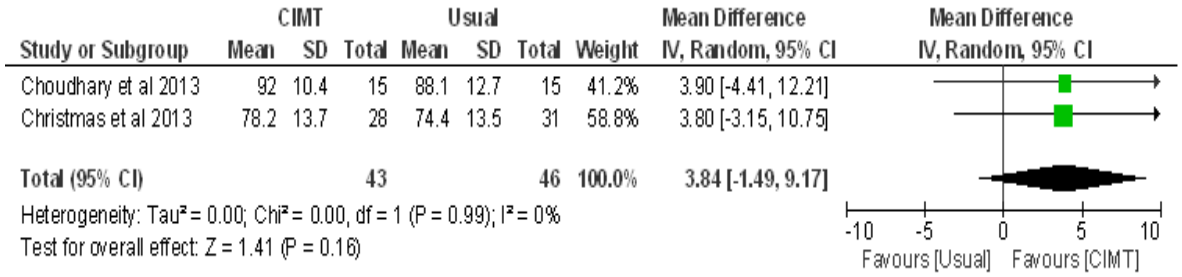


Figure 8.8. Meta-analysis of QUEST weight-bearing final value domain scores immediately post-intervention

The overall effect estimates for weight bearing favoured CIMT but not significantly (MD 3.84, 95% CI: -1.49, 9.17). Heterogeneity between studies was quantified (I^2 = 0%) and minimal. All estimates are shown in the forest plot in Figure 8.8.

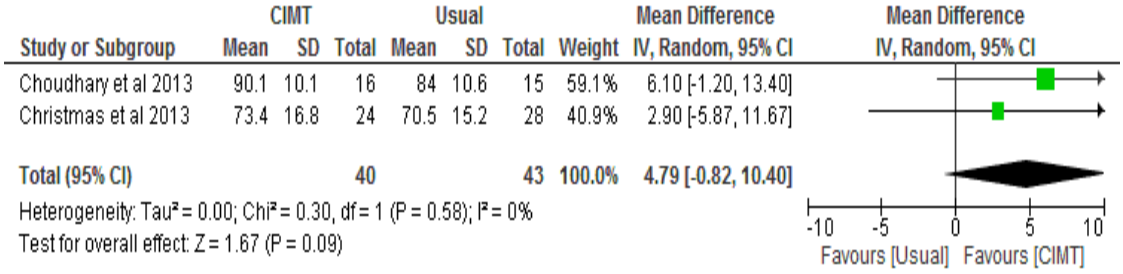


Figure 8.9. Meta-analysis of QUEST protective extension final value domain scores immediately post-intervention

Similarly, overall effect estimate demonstrated a greater treatment effect for CIMT (MD 4.79, 95% CI: -0.82, 10.40) but not statistically significantly for the protective extension domain scores. Variation in the observed estimates between studies, not due to chance, was quantified and the heterogeneity was I^2 = 0%. Each effect estimates and the overall summary effect are included in the forest plot in Figure 8.9.

In addition to the QUEST scores Fedrizzi et al. (2012) conducted motor assessment on the BESTA scale. This included a grasp sub-score which was pooled with the QUEST grasp domain score and is shown in Figure 8.10. Different scales were used therefore a standardised mean difference (SMD) computed. Combining scores using SMD revealed an overall treatment (non-significant) effect which favoured CIMT to improve grasp (SMD 0.20, 95% CI: -0.12, 0.51).

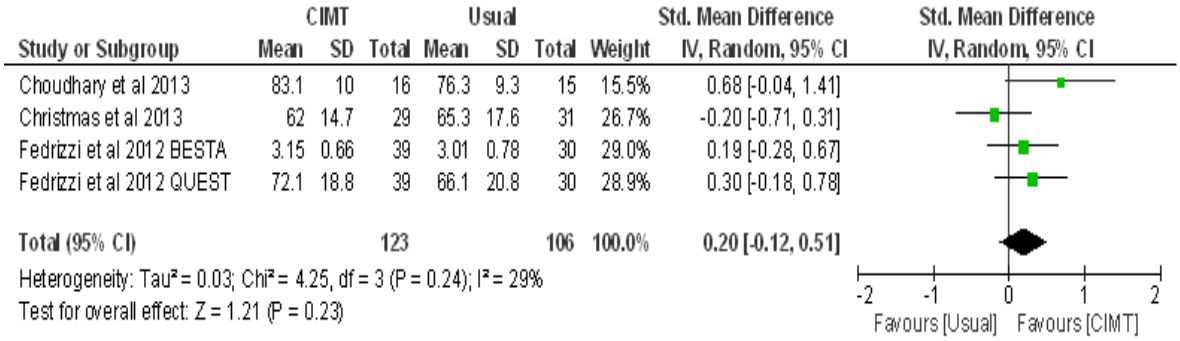


Figure 8.10. Meta-analysis combining QUEST grasp final value domain scores and BESTA grasp sub-score immediately post-intervention.

8.3.5.3. Health related quality of life measures

Health related quality of life (HRQOL) outcomes were also included in this systematic review and meta-analysis. Fedrizzi et al. (2012) included an activity of daily living (ADL) sub-score, as part of the BESTA scale. This was combined using SMD with the ADL dimension score from the PedsQL 3.0 cerebral palsy module in the CATCH trial. Mean change scores were unavailable therefore, final value scores immediately post intervention were combined. The summary effect, slightly favoured (non-significantly) usual care (SMD -0.25, 95% CI: –0.62, 0.12). The measure of

heterogeneity between the studies was measured (I^2 = 0%) and therefore, minimal. The effect sizes of individual studies and the summary effect size is shown in Figure 8.11.

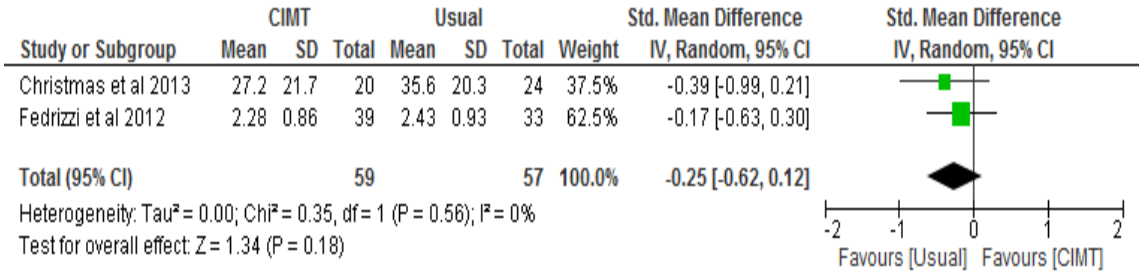


Figure 8.11. Meta-analysis combining the final value ADL dimension score from the Peds QL 3.0 cerebral palsy module and the ADL sub-score from the BESTA scale immediately post-intervention

The CATCH trial conducted HRQOL assessments at follow-up, therefore, the ADL -scores (final value scores) were combined at follow-up. The summary effect, slightly favoured (non-significant) usual care (SMD -0.13, 95% CI:–0.81, 0.54). The measure of heterogeneity between the studies (I^2 = 70%) suggested considerable variance between studies (Higgins and Green, 2011). The effect sizes of individual studies and the summary treatment effect size is shown in Figure 8.12.

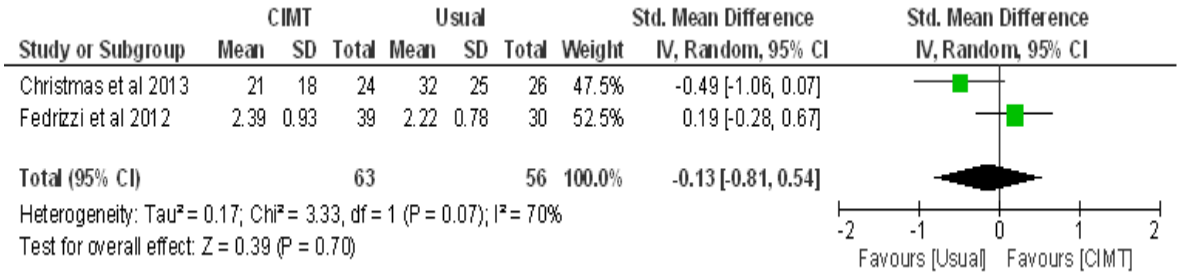


Figure 8.12. Meta-analysis combining the final value ADL dimensions scores from the Peds QL 3.0 cerebral palsy module and the ADL sub-score from the BESTA scale at follow-up.

8.3.6. Studies excluded from the meta-analysis

The cross-over trial conducted by Smania et al. (2009) and Abootalebi et al. (2010) were excluded from the meta-analysis. In the Smania et al. (2009) study the results of the first treatment period of this crossover trial were unavailable. The Abootalebi et al. (2010) study reported scores for the intervention group only.

8.4. Discussion

8.4.1. Summary of main findings

The aim of the review was to identify studies compatible with the CATCH trial and where possible synthesise data quantitatively in a meta-analysis to enhance precision. Eight studies were identified and data pooled from five. The primary outcome from the CATCH trial measured bimanual motor performance (i.e., usual practice; ICF; WHO 2001) using the AHA. The mean change scores from baseline were combined (Eliasson et al., 2005) and a treatment effect for CIMT was shown. Furthermore, the group difference (0.92 logits) revealed was equivalent to the smallest detectable difference (= 0.97) of the AHA. This was considered to represent a change in bimanual performance. This offers promising support for implementation of CIMT for the pre-school child with HCP within an NHS environment. Upper limb capacity data (i.e., best practice; ICF, 2001) were pooled from the CATCH trial with two other studies. (Choudhary et al. 2013; Fedrizzi et al. 2012).No treatment effect for CIMT was demonstrated. Similarly, health related quality of life outcomes were

combined (Fedrizzi et al., 2012; CATCH trial) immediately post-intervention and at follow-up and no treatment effects for CIMT were revealed

8.4.2. Limitations

8.4.2.1. Quality assessment

The included studies were judged by the quality assessment tool adapted from the Cochrane systematic review (Hoare et al., 2007) and found to be of varying methodological quality. Furthermore, study quality was affected by recruitment of small numbers of participants with no study reporting a prior power calculation leading to the possibility of imprecision (Higgins and Green, 2011). Small sample sizes were unsurprising given the prevalence rates of HCP (Johnson, 2002) but may be especially troublesome because of the heterogeneous population. A total of 262 were recruited with 240 included in the meta-analysis.

8.4.2.2. Meta-analysis

One synthesis (Eliasson et al., 2005) with the CATCH trial included in the meta-analysis (combining AHA mean change scores measuring bimanual performance) demonstrated a treatment effect for CIMT. The analysis demonstrated small confidence intervals and minimal heterogeneity providing some assurance. However, the result has to be viewed with caution. Eliasson et al., (2005) did not use a randomisation method for group allocation. Participants were assigned based on the geographical location of their residence and the results could have been influenced

by confounding factors (Sedgwick, 2014) such as the family compliance with treatment or the child's cooperation.

It might have been expected that combining bimanual performance on the AHA across the five studies would have similar results. This synthesis revealed moderate heterogeneity and two studies (Al-Oraibi and Eliasson, 2011; Fedrizzi et al., 2012) favoured usual intervention. The inconsistency may be accounted for by methodological variance and sample size. The study conducted by Al-Oraibi and Eliasson, 2011 had a 30% (6/20) dropout which was judged inadequate and although they did not specify group allocation this probably led to attrition bias. There was a considerable difference in this study across groups on baseline measures, probably due to the small sample size and heterogeneous population. The difference in outcome for the Fedrizzi et al. (2012) study may have related to the study design (a cluster RCT) which was not accounted for in the analysis.

The subjective nature of the assessments meant the outcomes could be open to distortion by an unblinded assessor (Sedgwick, 2011). Three studies (Choudhray et al., 2013; Al-Oraibi and Eliasson, 2011; Fedrizzi et al., 2012) included in the meta-analysis did not describe any procedures to maintain blinding of the assessors. Assessors had the opportunities to become unblinded from direct contact with the participants and their families or from the intervention therapists and other study personnel. This may have accounted for the inconsistency in the QUEST total scores. The CATCH data favoured usual intervention whereas the other studies (Choudhray et al., 2013; Fedrizzi et al., 2012) favoured CIMT.

Methodological difference across studies can led to inconsistency when combining data from different studies, however, clinical diversity relating to the intervention offered or the participants that are included may also contribute. The component studies of the meta-analysis excluded children based on different clinical presentations. For example, the degree of upper limb motor ability that was allowed varied considerably between studies. Choudhary et al. (2013) excluded children if they presented with a mild or severe motor disability. Whereas, Eliasson et al. (2005) included all levels of disability and therefore when included in a meta-analysis with the CATCH trial minimal heterogeneity was noted.

In the five included studies there was substantial variation in the CIMT intervention that was administered. The type of restraint (arm sling or wrist splint/cast), duration of restraint (2-24 hours per day), amount of daily therapy (1- 7 hours per day), intervention duration (4-10 weeks), the intervention environment (clinic setting or home) and administrators (parents and therapists) varied. The duration and type of restraint and training undertaken per study was considerably different which meant substantial variation in dosage. Indeed, Choudhary et al. (2013) described an intervention which offered a total of 66 hours whereas, Fedrizzi et al. (2012) offered 210 hours of CIMT. Therefore, although given the same label, the intervention undertaken between studies could vary widely. The synthesis conducted with Eliasson et al. (2005) and the CATCH trial demonstrated minimal heterogeneity however, a number of key clinical variables were similar. The intervention duration and environment (home) were comparable. Furthermore, the administration was

undertaken primarily by parents with guidance from therapists. Clinical diversity across CIMT studies was similar to a finding in a review of CIMT in children with HCP (Huang et al., 2009). In the 21 included studies they reported wide variability in the type of restraint (full-arm cast to gentle parental restraint), duration of restraint (1-24 hours per day) and intervention duration (1hour per week to 7 hours per day). They concluded that there was a lack of systematic comparison of the critical CIMT variables across studies.

8.4.2.3. Review limitations

There were a number of limitations of the review including the inability to obtain data from authors (Eliasson et al., 2011; Al-Oriabi and Eliasson, 2011) to include in a synthesis on mean change scores from baseline. This would have potentially enhanced precision, however both studies were methodologically flawed because of excessive drop outs with a small number of participants (n = 39).

8.5. Conclusion

The systematic review and meta-analysis evaluated CIMT implemented in a manner compatible with the intervention protocol of the CATCH trial. An existing Cochrane systematic review (Hoare et al., 2007) was updated with controlled trials which investigated CIMT in pre-school children with HCP. Data from the CATCH trial was combined with one other study (Eliasson et al., 2005). Although a treatment effect was demonstrated which indicated improvement in bimanual performance

immediately post-intervention, a number of questions remain. On balance especially in view of scant NHS resources it would be beneficial to conduct further research to support clinical implementation. The clinical diversity which has been reported in other reviews (Huang et al., 2009) means it is difficult to evaluate findings because of the lack of systematic comparison of key components. Future research should evaluate different features of CIMT including dosage, frequency and duration of interventions and administration. The methodological quality and sample sizes of the studies included in the review highlights the need for high quality trials with large sample sizes. Future trials should pursue short and long-term outcomes, be suitably powered and conduct, uniform reliable and valid assessments to allow consistency and pooling

Chapter 9: Discussion

9.1. Summary of main findings

The randomised controlled trial reported in this thesis compared two methods of constraint induced movement therapy (CIMT) to improve functional ability in the affected upper limb in pre-school children with hemiplegic cerebral palsy (CATCH trial). It investigated a new model of CIMT developed to be implemented within the NHS. It incorporated a prolonged restraint methodology and was delivered by families and nursery staff. It was successfully administered and evaluated in paediatric community NHS settings where these children usually receive their therapy. It was found to be safe, feasible and acceptable to families. Measures of fidelity revealed that the novel approach was a more effective method of treatment delivery.

Short-term motor outcomes were compared between the new technique and a usual NHS CIMT intervention. Although there was considerable inter-participant variability, both methodologies produced a statistically significant change in bimanual function. However, it was greater in the prolonged restraint group (effect size of 0.5 versus 0.2) but the between group difference was not statistically significant. The outcome data on bimanual performance from the prolonged restraint group was combined in a meta-analysis with findings from a similar study. The increased precision demonstrated a treatment effect on the Assisting Hand Assessment (AHA; Krumlinde-Sundholm and Eliasson, 2003; Krumlinde-Sundholm et al., 2007)

of 0.92 logits which is similar to the smallest detectable difference (0.97 logits) of the tool indicating actual change in bimanual performance.

Secondary motor outcome measures demonstrated no change on unimanual capacity for either group. However, outcomes reported by parents suggested there was a difference immediately post-intervention in bimanual performance in the group who received the new intervention but this was not sustained to follow-up. Health related quality of life (HRQOL) outcomes were measured. The usual NHS CIMT intervention was found to have had a negative impact at follow-up in the younger child (less than two-years) on the subjective health perceptions such as emotional and social functioning. Those children however who had received the novel intervention remained unchanged on these outcomes.

9.2. Related research

There has been little research conducted in the UK on children with cerebral palsy (CP) and this is reflected in the UK Clinical Research Network (2011) study portfolio database. The register contains 2408 studies but only 20, 0.8% has investigated or are currently investigating CP. The CATCH trial has provided an example of a successful scientific evaluation of this population. It is the largest trial conducted to investigate CIMT for the HCP population in the UK and one of the biggest worldwide. Additionally, it was successfully carried out in a community based NHS setting as part of usual NHS practice. This is where children with HCP typically receive their therapy. Experimental research does not usually include a fully generalisable account

to support implementation into different settings (Medical Research Council, 2006). However, the CATCH trial provided evidence that the intervention could be repeatable and transferrable into the NHS and provided evidence to guide future investigation.

9.2.1. Newly-developed intervention protocol

CIMT was originally developed for the adult stroke population (Taub et al., 1993; Taub et al., 1999) and consists of two distinct parts (i.e., movement restriction of the unaffected upper limb and therapy of the affected upper limb). Both components aim to induce intensive activity of the affected upper limb. Over time although the components have remained their features have been adapted based largely on cultural, organisational and financial factors. Furthermore, the target population has been extended to include children with hemiplegic cerebral palsy (HCP). This has altered variables such as the administration, frequency and duration of therapy and the type and intensity of the restraint (Eliasson et al., 2013). Indeed in the systematic review reported in this thesis the included studies described diverse protocols. For example, Choudhary et al (2013) offered a CIMT protocol which consisted of two hours of daily therapy for a four week period (66 hours in total) offered by a therapist and the parent. The movement restriction was enforced by an arm sling. Whereas, the participants in the Smania et al. (2009) study received eight hours per day of therapy over a five week period (200 hours in total). The restraint of the unaffected upper limb was provided by a wrist splint and the therapy was delivered primarily by parents. As long as the two components remain, adaptation of the CIMT protocol to meet local needs was considered an acceptable practice by an international group of

expert clinicians and researchers (Eliasson et al., 2013). They state that all existing models of CIMT could be used for further investigation.

A novel protocol of CIMT was developed and evaluated in the CATCH trial specifically to be implemented within an NHS environment because this is where children in the UK with HCP would generally receive their therapy. This was despite a standard NHS model of CIMT already existing. However, the standard approach was based on limited evidence and found to be difficult to administer (PC, JM patient, public involvement representative). Given the persistent nature of the movement restriction in the new model it was considered unsuitable for school children who would need to access the national curriculum. Especially because of the difficulty they may already have due to the motor and other disorder neurodevelopmental disorders including communication and behaviour associated with cerebral palsy (Rosenbaum et al., 2007). Therefore, pre-school children only were included in the CATCH trial.

9.2.1.1. Theoretical approach

CIMT aims to effect change at the function or activity level Novak et al. (2013) and was considered suitable for this group of children with limited activity (Rosenbaum et al., 2007) of the affected upper limb. The consistent feature of the CIMT models is that an opportunity for intensive practice with the affected upper limb is provided. The underpinning theory of how practice improves the child's motor performance is associated with motor learning. Although a number of theories exist, there are two

key approaches. The information processing approach (Adams, 1971; Schmidt, 1975) assumes a child's movement is based on pre-determined motor programmes (generalised motor programme). The programmes are learned from previous experiences and stored in memory. However, in the child with HCP the motor programmes have been predominantly conducted by the unaffected upper limb (effector). Therefore, there is limited possibility to experience and subsequently learn movement with the affected upper limb. CIMT has the potential to change how a movement is executed by changing the effector of the motor programme towards the affected upper limb. It is assumed that as movement with the affected upper limb is practiced and experienced more information is assimilated to develop and refine the memory.

According to the dynamical and ecological approach to motor learning (Fowler and Turvey, 1978; Newell, 1986; Newell,1991; Kelso 1995) movement is learned by the child practicing within the environment. Provision of substantial opportunity underpins the spontaneously developed coordinated movement patterns between the child, the task and the environment (i.e., to explore the environment and find the opportunities available or affordances). However, in HCP the reduced use of the affected upper limb minimises the opportunity. CIMT has the potential to shift exploration of the environment towards the affected upper limb and influence the development of coordinated movement patterns. The underlying assumptions from these approaches are fundamentally different. Both however, advocate mass practice of the affected upper limb to improve motor learning and subsequent motor performance. Therefore,

both motor learning theories provide explanation for improvement in motor performance of the affected upper limb following CIMT.

9.2.1.2. Type of restraint

The movement restriction of the unaffected upper limb in CIMT can be provided by a removable device (e.g., a sling, fabric mitt or splint) kept in situ at the same time as the therapy is administered. Application of the restraint can be conducted by a therapist or a parent/guardian or both. Conversely, a non-removable restraint, such as a plaster cast is applied by a therapist or plaster technician and remains in situ for a period of time.

A number of studies have investigated CIMT protocols which have administered a removable device. However, there have been reports of some difficulty with administration. For example, Wallen et al. (2011) investigated CIMT in young children aged mean (19 months) SD (10 months) with HCP (n=50). The protocol combined a removable fabric mitt to provide restraint and occupational therapy (OT) to the affected upper limb and was compared to OT alone. The interventions were administered by parents. Twenty percent (5/25) of the CIMT group participants demonstrated frustration and refusal to cooperate compared to 4% (1/25) in the OT group. Additionally, Eliasson et al. (2005); Al-Oraibi and Eliasson (2011) and Eliasson et al. (2011) investigated CIMT using a removable mitt to restrict movement primarily applied by parents. The studies demonstrated favourable results but in two studies (Al-Oraibi and Eliasson, 2011; Eliasson et al., 2011), 30% of participants

(6/20 and 6/18 respectively) dropped out. Conversely, studies that investigated CIMT with a non-removable restraint (Taub et al., 2004; Deluca et al., 2006; Case-Smith et al., 2012) reported minimal dropout of participants.

In the CATCH trial a non-removable method of restraint (i.e., a wrist cast or splint and bandage) was administered which was applied by the therapist and left in situ. It may be expected that a removable restraint device which is on for less time would be more tolerable and easier for the child to accept and family to administer than a non-removable device. However, a disadvantage of the removable device is that it has to be reapplied, usually by a parent each day. If the child is resistant this may be difficult for parents to manage and this may have led to the large number of drop outs in the (Al-Oraibi and Eliasson, 2011; Eliasson et al., 2011) studies. In the CATCH trial the prolonged restraint protocol included both the application and removal of the devise to be conducted by a therapist rather than a parent, except in an emergency situation. The decision was upheld by the excellent retention of participants on the CATCH trial with only one drop out from the 30 children randomised to the prolonged restraint group. Furthermore, a comparison of the amount of therapy delivered between the two restraint methodologies in the CATCH trial demonstrated that the non-removable restraint was a more effective means of delivering therapy than the intermittent manual restraint. The findings from the CATCH trial have provided support for the use of CIMT with a non-removable restraint applied by therapist in a full-scale trial.

A disadvantage of the non-removable restraint was related to its continuous nature, which may lead to adverse events. For example, Deluca et al. (2006) applied a full arm bivalved fibreglass cast for 21 days, which was removed once a week. They reported minor skin irritations for three (3/18) children, which improved with medicated ointment. Similarly, Taub et al. (2004) administered the same restraint technique and described four (4/9) participants with mild skin redness, a rash or pinching. They were treated effectively with medicated cream. The possibility of adverse reactions was kept to a minimum in the CATCH trial. The size of the restraint (i.e., a short-arm rather than long-arm cast) meant the area that was immobilised was reduced. In addition, the restraint device was well padded and the material to enclose the fingers was a soft crepe bandage with less potential to rub the skin.

Another possible adverse event was the increased risk of the child hurting themselves if they feel, because the saving reactions with the unaffected upper limb were compromised. However, this was also kept to a minimum because of the size (short-arm) of the restraint. There were 12 non-serious adverse events reported in the CATCH trial. They were either a minor skin abrasion or superficial bruising from a fall. All resolved quickly. It would be expected that in this age group of children, as part of normal life they may have frequent falls or bruising. A procedure for reporting and recording adverse events in the CATCH trial was instigated. This allowed a timely response and an independent review of adverse events was conducted by a Trial Steering Committee. The adverse events did not lead to any drop-outs or the trial being terminated early which suggested it was a safe procedure.

The permanent nature of the restraint in the CATCH trial meant there was potential for a functional deterioration in the immobilised upper limb. An independent assessment of the immobilised limb evaluated whether the restraint had had an adverse effect on function. All participants were found to have had no functional deterioration from immobilisation at the ten-week QUEST assessment. This was a similar finding to Deluca et al. (2006) who reported no functional changes following immobilisation. The information from the CATCH trial indicated that the non-removable restraint was a safe intervention and the procedures implemented for governance were satisfactory and suitable for a definitive trial. It was anticipated that the continuous nature of the restraint, may lead to frustration, however, it did not lead to families dropping out which suggests it was manageable. For a full-scale trial a description of the adverse events that occurred in the CATCH trial should be included in the patient information sheet to enhance informed consent.

9.2.1.3. Administration

The interventions in the CATCH trial were administered primarily by parents/guardians and nursery workers and guided by therapists in the child's usual environment. This mode of administration is common in CIMT investigations and the administration of other therapies in the NHS. The excellent retention rates of the participants suggested the methodology was acceptable to the administrators. This was particularly impressive considering the client group. These families potentially have huge demands placed on them managing a child with HCP which does not only mean a physical disability but there may be secondary problems as described in the definition of cerebral palsy (Rosenbaum et al 2007). For example, 4% (3/62) children

in the CATCH trial also had epilepsy. Additionally, the outcomes in the CATCH trial indicate successful enactment of the CIMT interventions and support the competence of the parents/guardians and nursery staff in administration. Previous research Novak et al. (2009) demonstrated similar findings. They investigated the implementation of an occupation therapy home programme for children with cerebral palsy (n = 36) and a mean age (7 years 7 months), developed collaboratively and delivered by parents in the home environment. A significant effect size of 1.4 (95% CI: 0.6 –2.2;, p = .01) for the treatment group at the 8-week primary end point was demonstrated.

9.2.2. Variability in outcome

Bimanual performance in the CATCH trial improved across both groups following the interventions. However, when the performance of individual participants was evaluated there was considerable variability in outcome. A number of participants had outcomes which demonstrated no change in bimanual function (i.e., less than the smallest detectable difference). This suggests there may be a number of contributing factors affecting outcome. To explore possible reasons, a regression analysis (including age, degree of impairment amount of therapy actually delivered and child cooperation) was conducted on the performance outcomes at ten weeks. However, this did not provide any answers as none of the variables had a statistically significant impact on outcome.

Alternative explanations could be that the outcome was affected by an unmeasured variable such as the compliance of the family to the intervention (this was important because of the reliance on the family for administration). Therefore, poor compliance may have affected outcome. Conversely, it may be associated with the reason the child does not use the affected upper limb. Children whose bimanual performance did not change may be already using their upper limb to its full capacity (i.e., best available; ICF). For example, the limited activity including grasp (Eliasson et al., 1995) and release (Eliasson and Gordon, 2000) may already be being used at the full potential. However, other children may have more potential but chose to "actively suppress" or avoid using the affected upper limb because movement is difficult and clumsy (developmental disregard; Taub, 2004). CIMT forces the child to perform in a way that is closer to their capacity which may provide the opportunity to change motor skill and performance. Eliasson and colleagues (2005) in their study on young children with HCP also found the bimanual performance of the CIMT group changed significantly compared to no intervention but there was considerable within group variability.

It could be argued that the poor responders should be excluded from any future definitive trial. However, this poses a number of problems. Firstly, it can be difficult to identify the children who will have poor outcomes. This is because although activity measures may identify poor function they do not necessarily provide reasons why the response is limited. Furthermore, the children who were defined as poor responders were those whose change in bimanual performance was not large enough to represent a difference in bimanual performance (i.e. less than the smallest detectable

difference). However, this does not necessarily mean the change was not clinically important. The size of change that would suggest a clinically meaningful difference is more complex and has not yet been established for the AHA (Krumlinde-Sundholm, 2012). Indeed, small changes can be important for the child and family, if they led to functional gains. For example, a change in just one item such as “how the hands coordinate together” could improve the ability of the child to self-feed. It would be recommended, therefore, that a definitive trial should include all levels of motor ability to enhance generalisability of the findings.

9.2.3. Dosage

The amount of practice administered across both groups in the CATCH trial was sufficient to effect a change. However, a threshold effect dose (i.e., the amount required to produce a change) was unclear. The outcomes from other CIMT studies could be investigated to further inform dosage. This can pose problems however, as highlighted in the systematic review reported in the thesis because of the diversity of protocols. For example, dose may be varied but also intervention administration may be different such as frequency and duration. Therefore, the interaction between these factors has to be considered. Especially important for future research is to investigate the intervention characteristics, as well as the possible existence of a threshold effect dose.

In the CATCH trial there was a larger effect on bimanual performance in the prolonged restraint group which may be explained by the higher amount of therapy

delivered to the child. This finding might be expected when related to the literature. For example, the randomised controlled trial conducted by Kwakkel et al. (1999) investigated a cohort of patients with recent onset stroke. They found that more therapy led to a greater functional change. They compared intensive arm training (30 minutes per day, five days per week for 20 weeks) of the affected upper limb with a control group who had their limb immobilised for a similar time period. A statistically significant difference which favoured the intervention group was reported in upper limb dexterity.

To date there have been few studies that have examined the impact of CIMT dosage and the results are inconsistent. For example, Gordon (2011) compared dosage (60 hours over 10 days versus 90 hours for 15 days) in two separate HCP studies (Gordon et al., 2007; Gordon et al., 2011). A unimanual test of hand function (Jebsen et al., 1969) improved more with a higher dose. Conversely, Case-Smith et al. (2012) administered CIMT delivered for 21 consecutive days to two separate groups. All aspects of the intervention were the same other than one group received three and the other six hours of one-to-one therapy. There was no difference in upper limb gains reported across groups. Although, a possible confounding factor was the non-removable restraint which meant unstructured practice could have occurred outside of the therapy time. The impact of dosage of CIMT to outcome requires further evaluation in a definitive trial.

The amount of practice undertaken by standard NHS CIMT (manual restraint) was enough to effect a change in bimanual performance. This was surprising considering

the difficulty found with administration of this model. It may be explained by the inclusion in the standard intervention of fidelity measures which are not part of the intervention in usual practice. However, the change in bimanual performance in this group suggests that the CATCH trial was underpowered to demonstrate a treatment effect for the novel intervention. This has implications for a definitive trial and suggests a comparison should include a no intervention group such as a waiting list control.

9.2.4. Use of outcome measures

The outcome measures in the CATCH trial matched the expected effects from this activity based intervention and included measures on bimanual performance. The Assisting Hand Assessment (AHA; Krumlinde-Sundholm and Eliasson, 2003; Krumlinde-Sundholm et al., 2007) has been the measure of choice in a number of studies investigating CIMT. It has demonstrated positive treatment effects (Eliasson et al., 2005; Al-Oraibi and Eliasson, 2011; Eliasson et al., 2011). However, one difficulty has been the inconsistency of the reporting of results with different scores used by different studies which has prohibited pooling results. This was the case in the meta-analysis reported in this thesis. It has been recommended that future studies, report the Logit-based, 0-100, AHA unit score (Eliasson et al., 2013).

A measure of upper limb unimanual capacity the Quality of Upper Extremity Skills Test (QUEST; Dematteo et al., 1992) was included in the CATCH trial. No change was demonstrated. It was difficult to speculate why there was no change because the training offered with CIMT focuses on unimanual skills as it is undertaken with the

restraint in situ. However, it needs to be remembered that the CATCH trial was powered, based on outcomes for bimanual performance. Therefore, it may have been underpowered to detect a change in unimanual capacity. Other CIMT studies which measured outcome on unimanual capacity have shown inconsistent findings. Choudhary et al. (2013) demonstrated a statistically significant improvement measured with QUEST after four weeks of CIMT in their randomised controlled trial on young children with HCP. Whereas Deluca et al. (2006) showed no change on a similar group after three weeks of intervention. Guidelines for future CIMT research in the child with HCP recommend that although improvement in bimanual performance is the goal the training occurs on unimanual capacity. Therefore, both outcomes need to be evaluated (Eliasson et al., 2013).

The predominant neurological feature of individuals with HCP is spasticity. Therefore, it could be argued that the outcomes should have included measures of spasticity. This is especially in view of the bi-directional and interconnected relationship between impairment and activity described in the ICF. However, it is recognised that spasticity does not tend to exist in isolation but instead can co-exist with other motor disorders (weakness and dystonia; NICE, 2012). Indeed, Sanger et al. (2003) suggested many children with a primarily spastic clinical presentation will have some degree of dystonia and this is commonly seen in the upper limb in HCP. The relative contribution of separate impairments on activity can be difficult to gage. Is the child unable to grasp because they have weak finger flexors or spasticity that resists movement? Furthermore, the clinical presentation can be further complicated by growth which may change muscle length and delay in maturation (Sanger et al.,

2003). Additionally, spasticity can have an inverse relationship to function. In cases where there is coexisting weakness the resistance it offers may help function conversely, the associated hypertonus can lead to severe disabling muscle contracture (Sanger et al., 2003). Perhaps it is unsurprising that when studies have included activity and spasticity measures there have been minimal correlation between the outcome measures. Charles et al. (2006) in their study on children (n = 22) with HCP (mean age 6 years,8months) found that motor activity performance showed improvement following six hours of daily CIMT for a period of ten days but measures of spasticity were unchanged. Spasticity based measures should not therefore be included in a full-scale trial.

It is important that parental self-reported opinion which has the potential to provide knowledge about the users own perceptions of the intervention is provided in a definitive evaluation. This was considered important and suggested by an international group of expert clinicians to be included to measure the effectiveness of CIMT in future research (Eliasson et al., 2013). This was conducted in the CATCH trial by the completion of a parent-reported motor outcome measure the Birmingham Bimanual Questionnaire (BBMQ). For a definitive trial a measure such as the BBMQ would be administered. However, it would not replace but complement another motor assessment, such as the AHA. Furthermore, it does need to be remembered that parent self-reported assessments can pose some difficulty because of the awareness of group allocation and the possibility of distortion of the outcome (Sedgwick, 2011).

The goal of any rehabilitation intervention is to influence the effect it has on the patient's ability to participate in life situations. Activities of daily living such as dressing and feeding and integration into an educational setting would be especially relevant to evaluate. Health related quality of life (HRQOL) assessments were included in the CATCH trial. However, they were inconclusive and viewed with caution primarily because of the small sample sizes which meant the evaluation was underpowered. A definitive trial would aim to include self-reported outcomes such as HRQOL using an appropriate sample size.

9.3. Limitations

In 8% (5/60) of cases in the CATCH trial the assessor was unblinded to group allocation which could have led to assessment bias and an overestimation in favour of the prolonged restraint (Day and Altman, 2000). The CATCH trial was particularly vulnerable because of the subjective nature of the outcome measures. A second assessor could not be used as funding was not available.

The assessor in the CATCH trial was involved in a number of aspects of the trial therefore, was exposed to unintentional unblinding by other people and the environment. Indeed, three of the five unblindings were through the intervention therapists. To minimise the risk of unblinding in a future trial the assessor should be independent and not involved in any other aspects of the trial. Furthermore, PC had contact with the participant in the CATCH trial during the ten-week assessment which led to her guessing group allocation for two participants. The implication of the

assessor guessing the allocation rather than actually knowing it is probably different (Boutron et al., 2004) with possibly less impact in the former. Therefore, was reported separately. Certainly, a guess can be incorrect. However, it would be recommended in future studies to minimise this as far as possible.

A number studies investigating CIMT (Eliasson et al., 2011; Al-Oraibi and Eliasson, 2011) have kept contact between the assessor and participant during assessment to a minimum. The primary outcome in these studies was the AHA however, it was conducted by one blinded assessor administering the AHA (which was video recorded) and, a different blinded assessor scoring the video recording of the assessment. This reduced the risk of the assessor scoring the AHA being unblinded by contact with the participant, by contact with other people during the assessment and exposure to the assessment environment. This method of assessment would be recommended for a future trial.

Although most measures to protect the group allocation were introduced at the beginning of the trial, two were protocol amendments (a reminder not to disclose group allocation was left on the assessor's (PC) phone and email and adverse events were reported to the trial coordinators rather than PC). This underpins the importance of a pilot trial for informing a definitive design.

There was an unexpected improvement in the bimanual performance in the NHS CIMT comparator group which demonstrated a significant improvement from baseline. This proposes that a limitation of the CATCH trial was that it was

underpowered to demonstrate a treatment effect for the novel intervention. This has implications for a definitive trial and suggests that a full scale trial should be appropriately powered for both short and long term outcomes. Furthermore, a no-intervention comparison group such as a waiting list control would be more appropriate to demonstrate an effect with the novel CIMT intervention for future studies.

The improvement in bimanual performance in the NHS CIMT comparison group may have been influenced by the inclusion of measures of treatment fidelity (diary and questionnaire), enhancing treatment delivery and leading to a greater improvement in outcome. These measures would not be administered in usual clinical practice but in the CATCH trial included for consistency across groups. The diary expected the administrators to complete a daily log which may have particularly influenced fidelity to the treatment and resulted in more treatment delivery. This supports the findings by Law and King (1993). They investigated compliance to home therapeutic interventions for children with cerebral palsy and found that completion of a daily log, by parents, was significantly correlated with the main predictor of therapy outcome (i.e., parents, self-rating of compliance). Although considered a limitation in the CATCH trial this finding does have implications for enhancing usual NHS clinical practice. The inclusion of treatment fidelity measures may improve the delivery of usual NHS interventions such as NHS CIMT and therefore, warrants further investigation.

The fidelity to treatment measures included in the CATCH trial were considered to have led to an enhancement of the treatment delivered in usual NHS CIMT practice. They included information on the amount of treatment that was actually delivered compared to what was planned (Carroll et al., 2007). This was assessed by parents/guardians and nursery workers reporting the intervention delivered as a proportion of that prescribed in a daily diary and from a weekly interview. However, this information has to be approached with some caution because it was reported rather than observed therefore, there could be some inaccuracy or distortion. It would be recommended in future studies that additional means of data collection be included. This could include the therapist taking more responsibility for the data collection through more frequent one-to one sessions to observe administration, either at home or at a clinic.

Treatment fidelity is not only about recording the amount of intervention delivered but also about its authenticity compared to what was intended (Hoffman et al., 2014). This can be especially important if the intervention is complex and consists of a number of components, such as CIMT. Although the interventions delivered in the CATCH trial were recorded, no other measures were incorporated to enhance the intended treatments. Therefore, fidelity to treatment was limited in the CATCH trial as a result primarily of the financial and time restrictions imposed in a PhD project. Recommendations to ensure the intended treatment is delivered have been provided by the Treatment Fidelity Workshop of the National Institute of Health Behaviour Change Consortium (BCC; Bellg et al., 2004) . They consist of key areas including;

training the intervention providers, evaluation of the intervention sessions, strategies for monitoring receipt of treatment and enactment of treatment skills.

Measures of treatment fidelity have already been described in the literature for CIMT investigations. To evaluate treatment sessions in the CIMT study conducted by Case-Smith et al. (2012) therapists not only collected daily treatment logs that included frequency and type of skills practiced but they also videoed the sessions. Furthermore, Eliasson et al. (2011) enhanced treatment fidelity from their earlier study (Eliasson et al., 2005) by providing a ten-step model for intervention clarification and structure to promote treatment enactment. They included guidelines on intervention preparation (discussion with family about intensive training method), execution (choice of activities) and follow-up (inclusion of feedback to family and pre-school).

Procedures to enhance fidelity to treatment using guidelines such as those provided by the BBC (Bellg et al., 2004) would be recommended for a definitive trial. Two areas in the CATCH trial of particular concern included the limited training provided for the intervention administrators (parents/guardians and nursery staff) and the unstandardised intervention environment. The qualitative analysis reported in the thesis did provide some insight from the perspective of the administrators and could therefore inform any measures incorporated. It highlighted the need to extend training to include behaviour modification to deal with the emotional reaction of the child to the interventions. It was also recommended that further qualitative research would be of benefit to access different levels of understanding, using a range of

methodologies. This could further inform the training and advice provided. In addition, measures to standardise the intervention environment could be incorporated. This might include conducting sessions in a clinical environment such as a children's centre and providing more guidance form a therapist. A CIMT tool kit could be offered which included written instructions and a range of suitable toys. However, care would be needed to ensure that any measures that were incorporated did not impact on the excellent recruitment and retention rates in the CATCH trial and considered the resource implication.

9.4 Research implications

The CATCH trial was the first stage in development of a novel methodology of CIMT suitable for use in an NHS environment in the pre-school HCP population. Based on the positive short-term outcomes and the synthesis of the results in a meta-analysis, further research is warranted. CATCH was successfully conducted in the NHS setting where children with HCP typically receive their therapy. This suggests that future research could be conducted in this environment. In addition, it has provided invaluable evidence to inform a definitive evaluation. Future investigation should include a full range of motor disability. The evaluation should include the use of valid and reliable outcome measures of upper limb activity (performance and capacity), participation and parent-reported outcomes. However, refinement of the methodology to enhance treatment fidelity is required before a definitive trial is conducted. Further qualitative analysis of the intervention from the administrator perspective would be invaluable to inform this refinement.

An unexpected finding in the CATCH trial was the improvement in bimanual performance with a usual NHS CIMT intervention. This suggests that the study was underpowered to demonstrate an effect with the novel CIMT intervention. Future studies to investigate the treatment effect of the prolonged restraint methodology should be appropriately powered for short and long term outcomes. Furthermore, a no-intervention group comparison group should be included, such as a waiting list control.

9.5. Clinical implications

The trial reported in this thesis demonstrated that the novel approach developed for an NHS environment was safe, feasible and acceptable to families. The novel intervention is repeatable and transferable into the NHS. It demonstrated short term improvement in bimanual performance. However, a number of questions remain before implementation of this novel model of CIMT into clinical practice. This includes the long-term outcomes of the intervention and the effect of dose especially in terms of the existence of a threshold effect dose and the impact of increasing dosage. Furthermore, the impact of intervention characteristics such as frequency and duration require investigations. It is expected that this is a low cost treatment, because of the utilisation of parents and nursery staff to administer the intervention with the potential for high returns. However, an understanding of the cost benefit of the intervention is required to inform implementation into practice therefore, a definitive trial should include a health economic analysis.

9.6. Conclusion

This thesis has shown that a novel approach to CIMT is effective in improving bimanual function in the short-term in the young child with HCP. Furthermore, it is safe, acceptable to families and provides an enhanced mode of delivery of therapy than usual NHS CIMT. The CATCH trial represents the largest trial ever conducted in CIMT in the HCP population in the UK. It was conducted in a paediatric community NHS setting where these children usually receive their therapy. The excellent recruitment and retention of participants has shown that the evaluation was feasible. Therefore, further research is possible and warranted and what is more the CATCH trial has provided evidence that the intervention could be repeatable and transferable into the NHS. This trial has contributed important knowledge to the field of CIMT in HCP and has the potential to influence further research for a definitive trial. Moreover, paediatric therapeutic interventions for cerebral palsy are generally poorly evidenced. However, the CATCH represents experimental research with a fully generalisable account which has the potential to influence investigations into other therapeutic interventions for cerebral palsy, to both grow the evidence base and offer developments in clinical practice.

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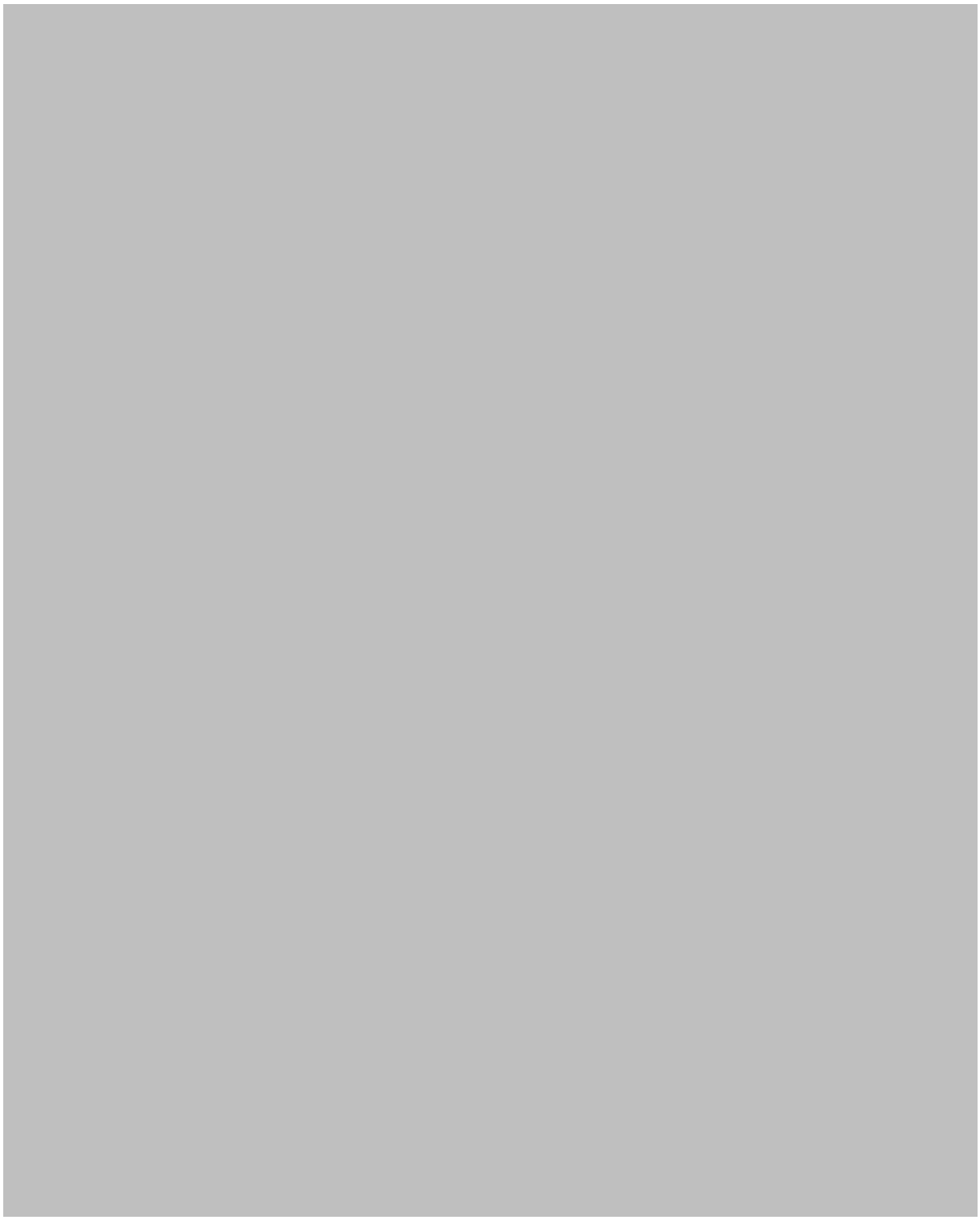
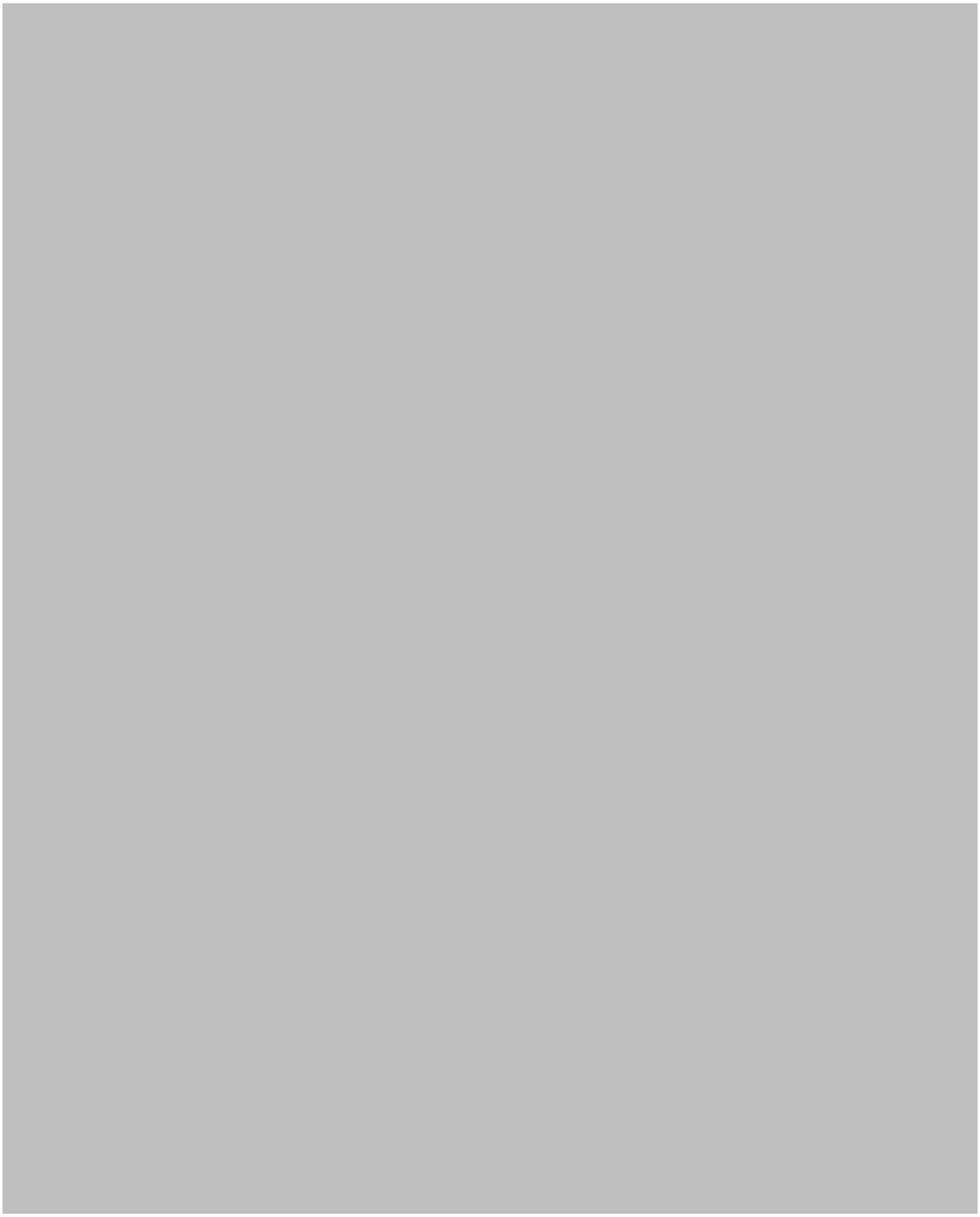
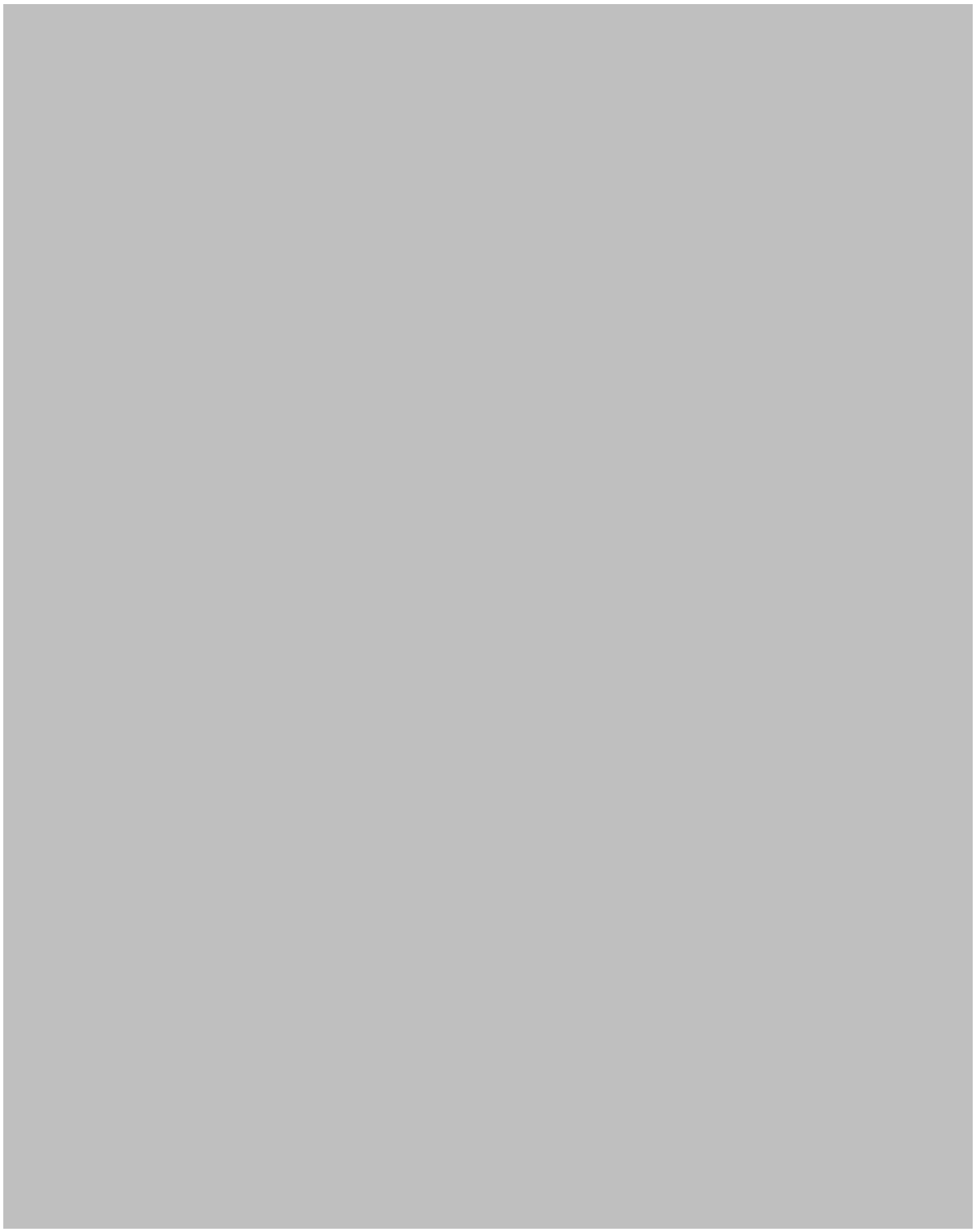
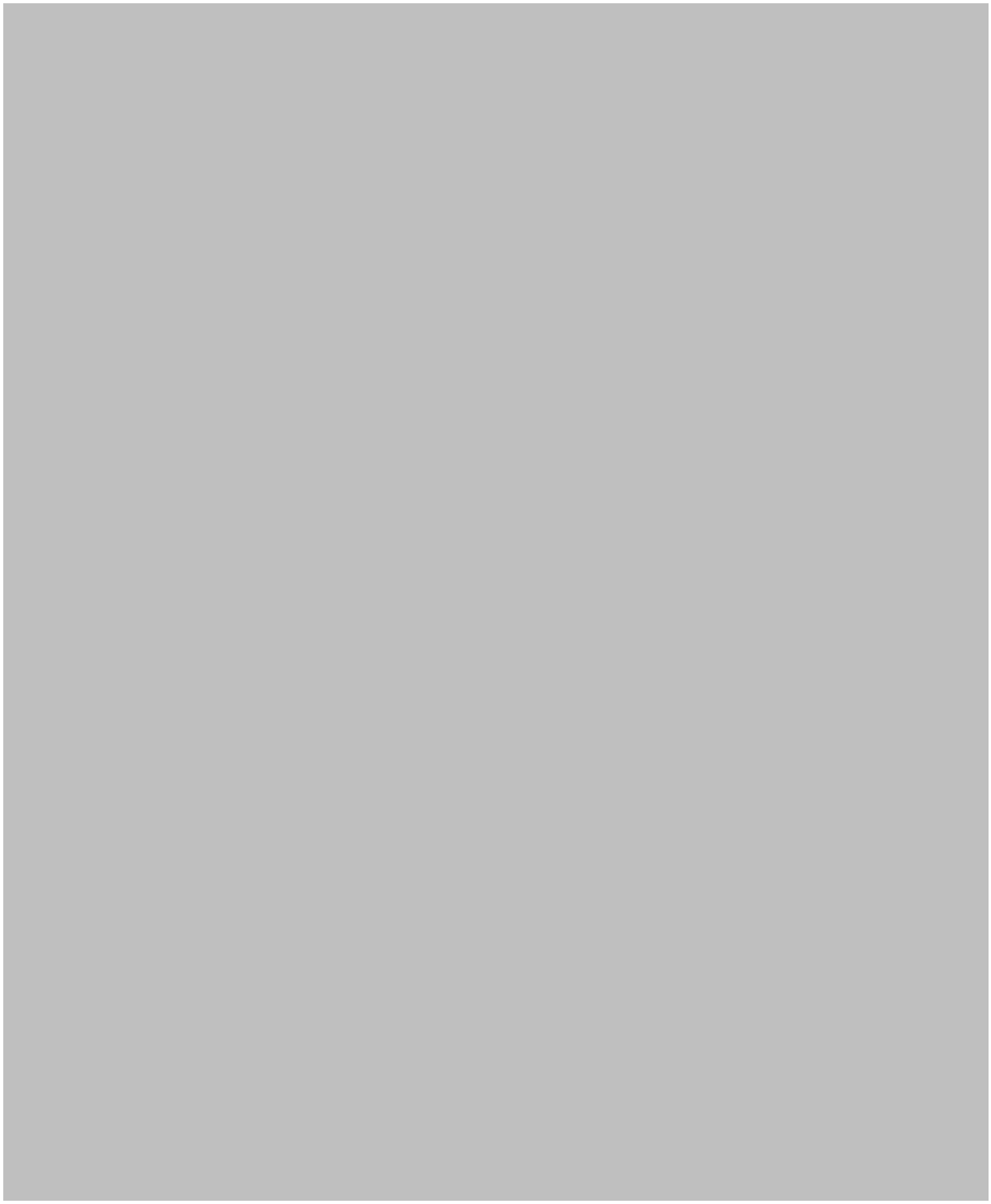
Appendix 1

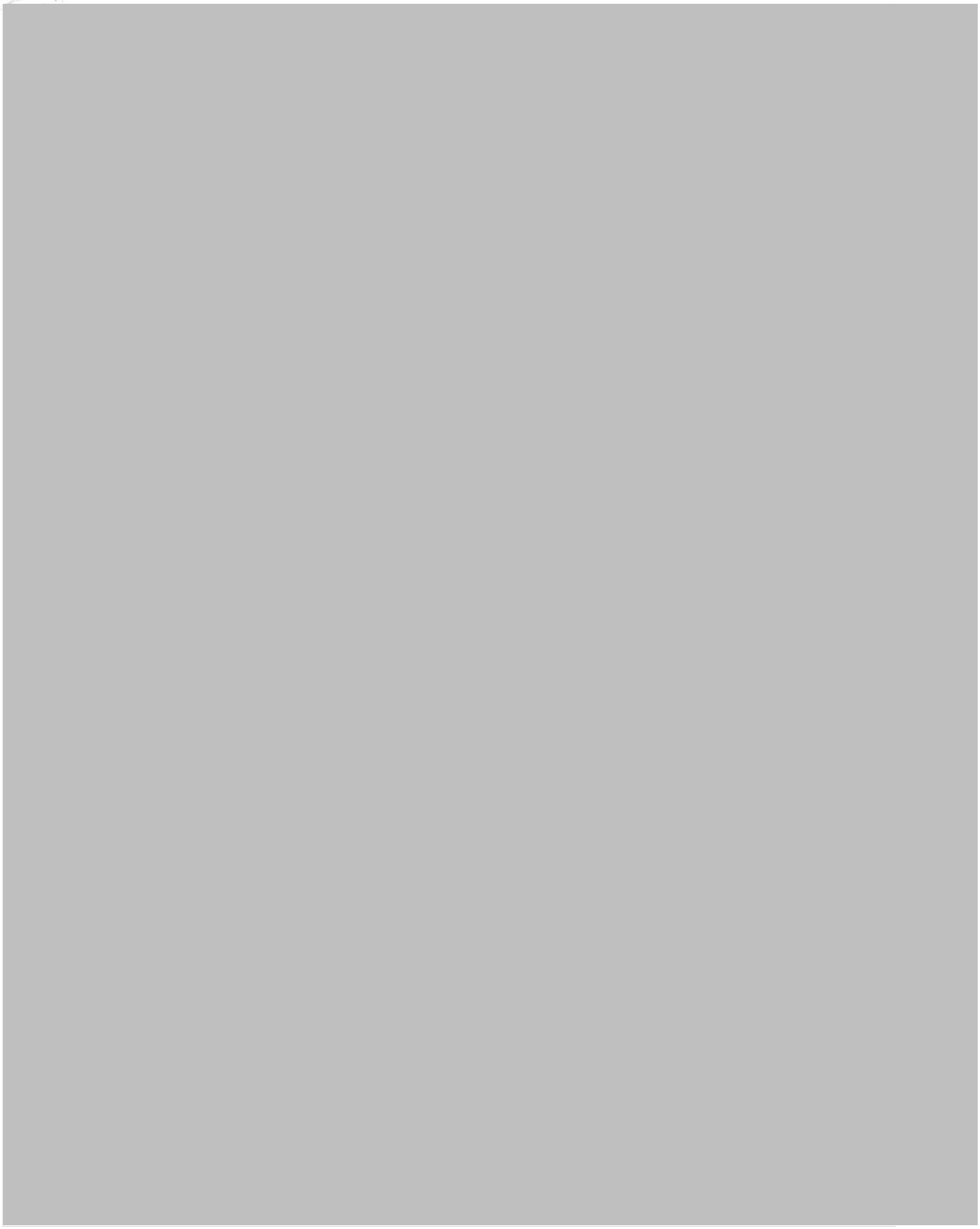
- Ethical approval
- Substantial amendments
- Sponsorship
- R&D Trust approvals

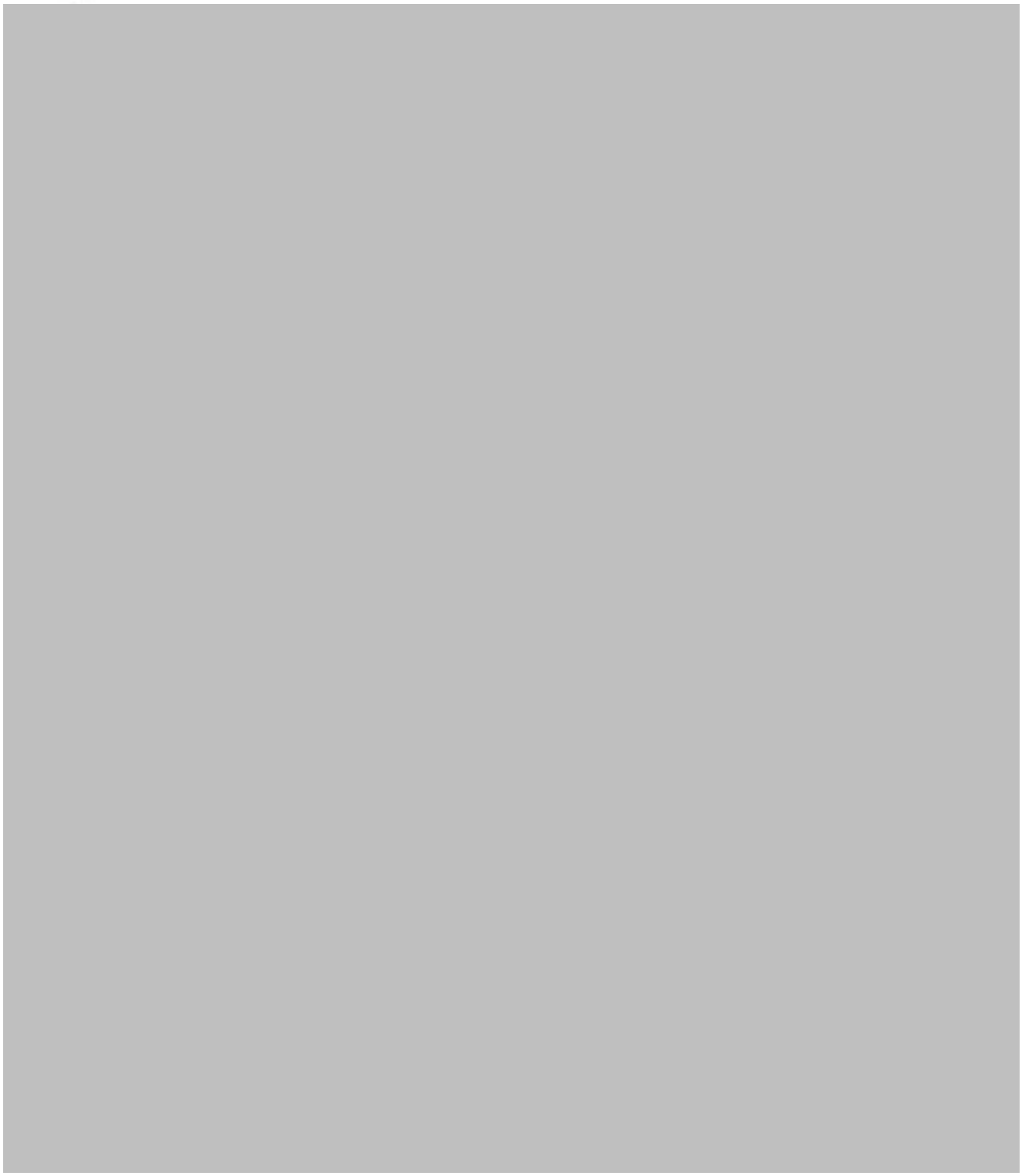


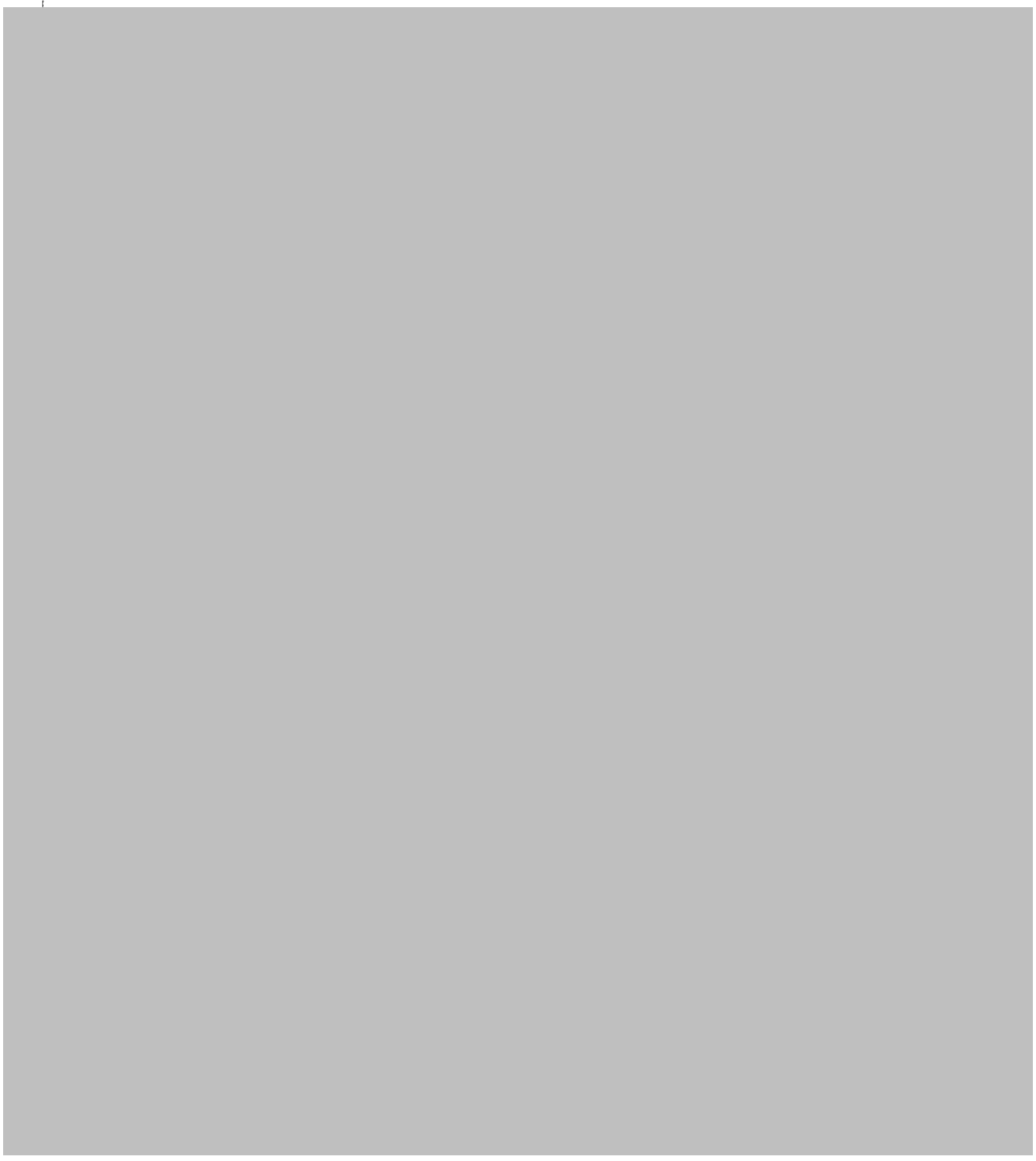


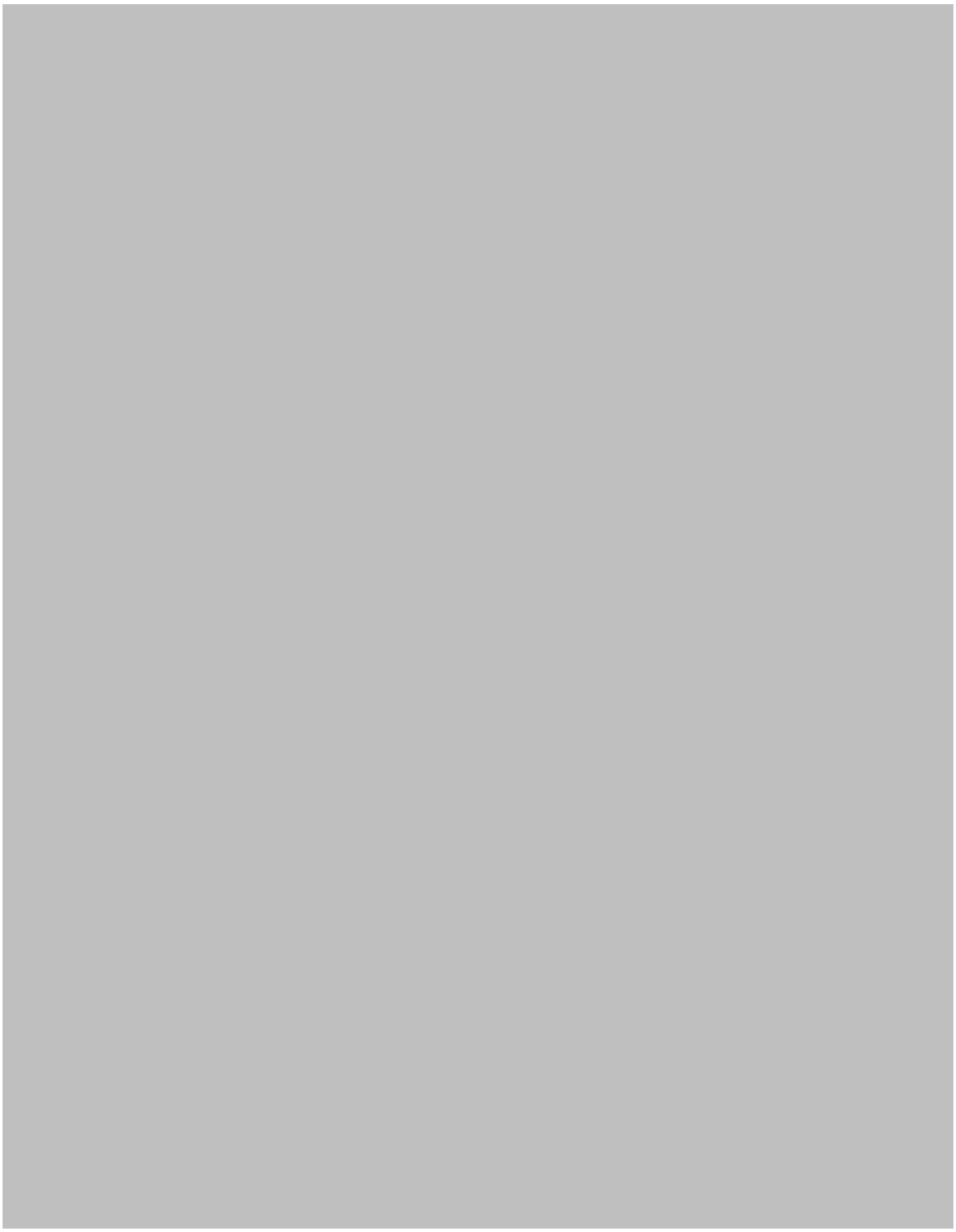


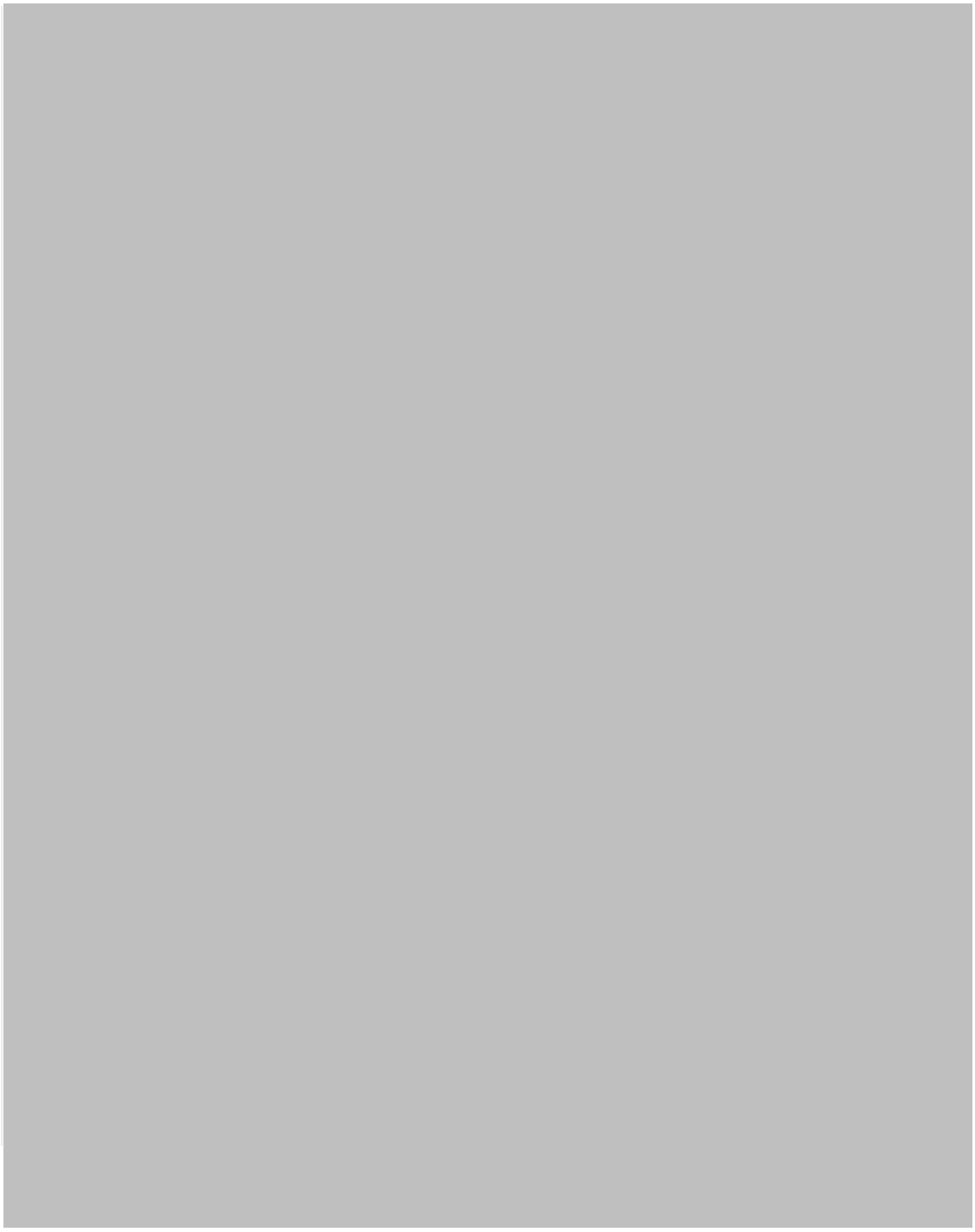


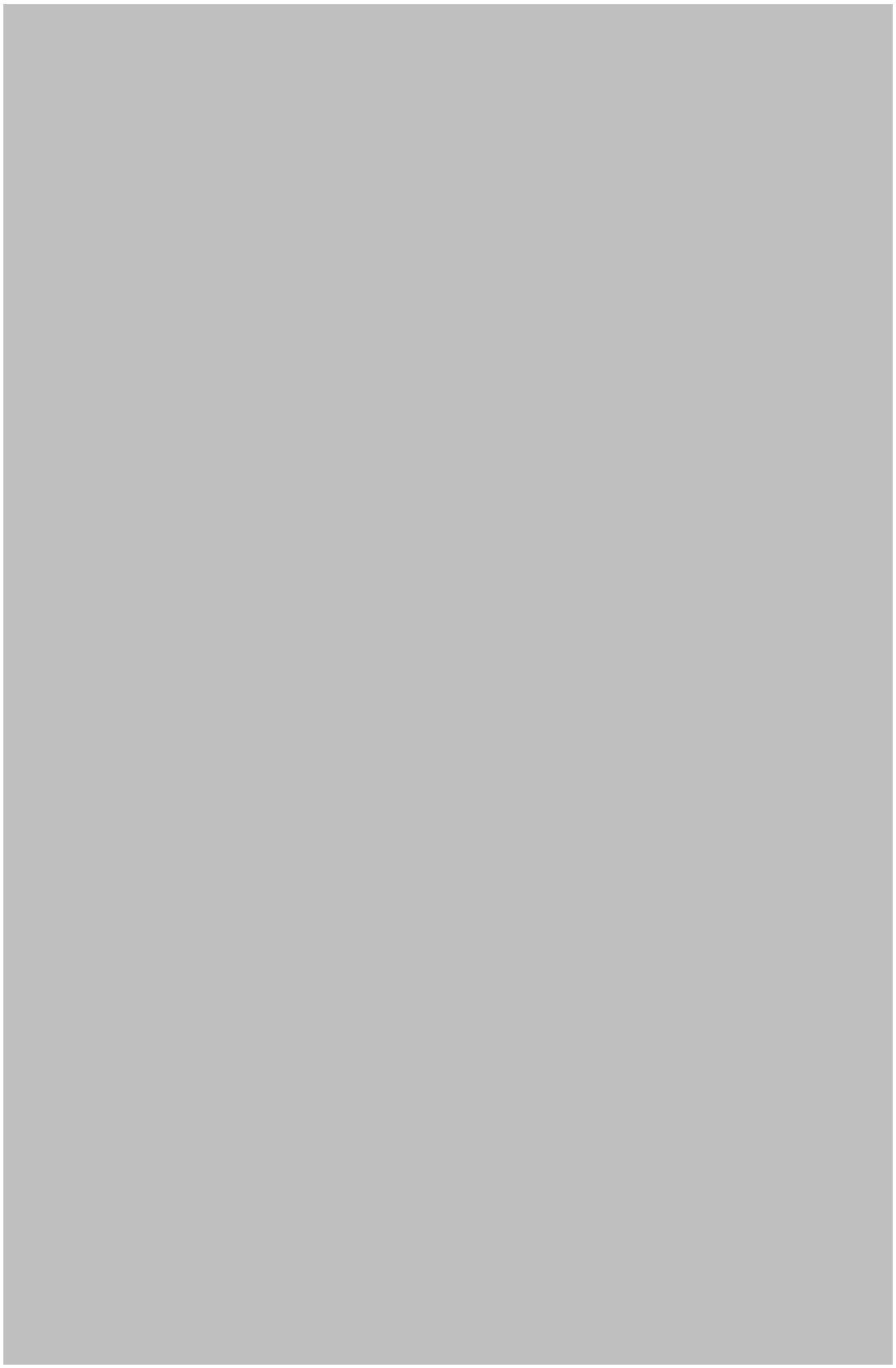


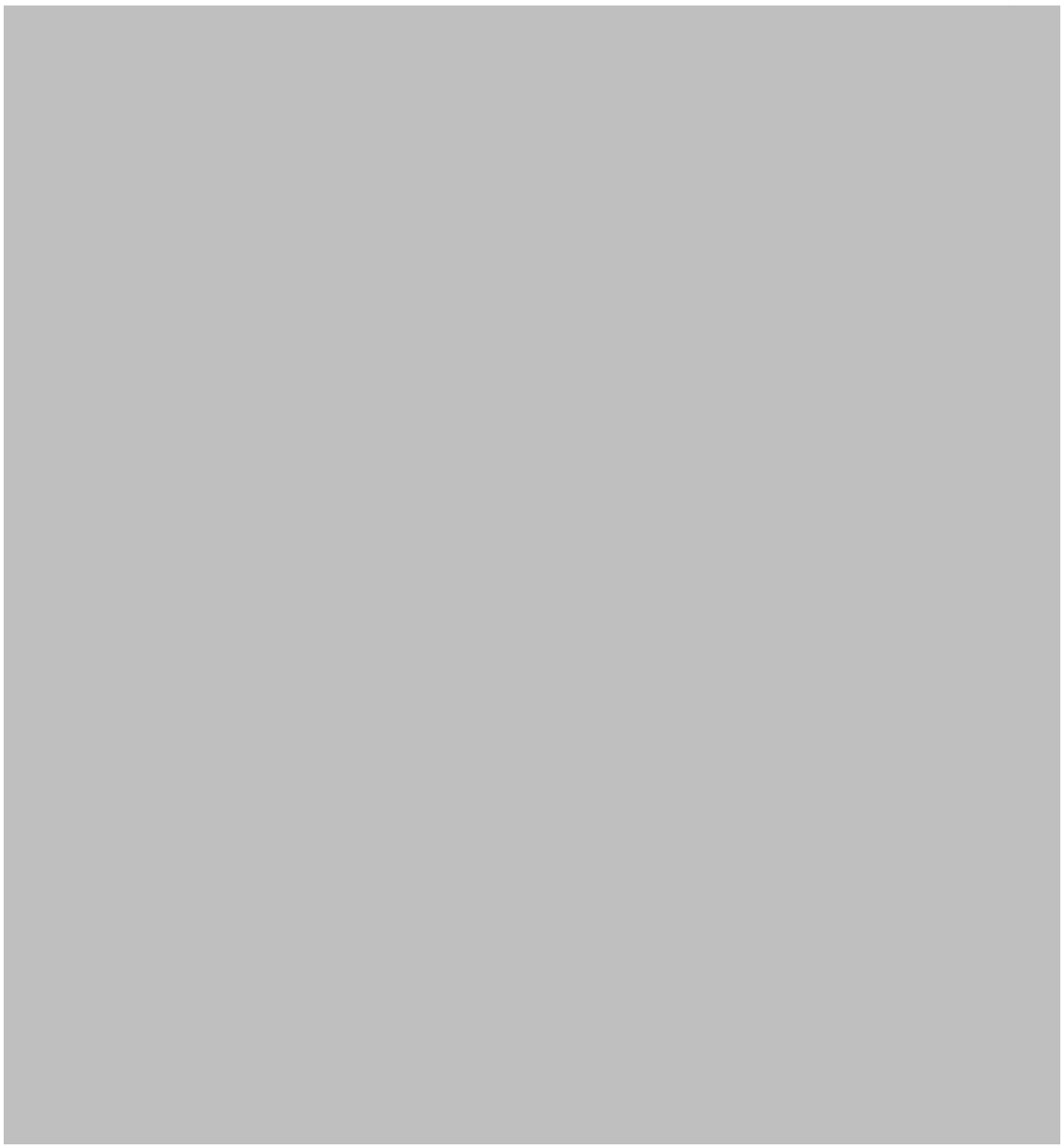


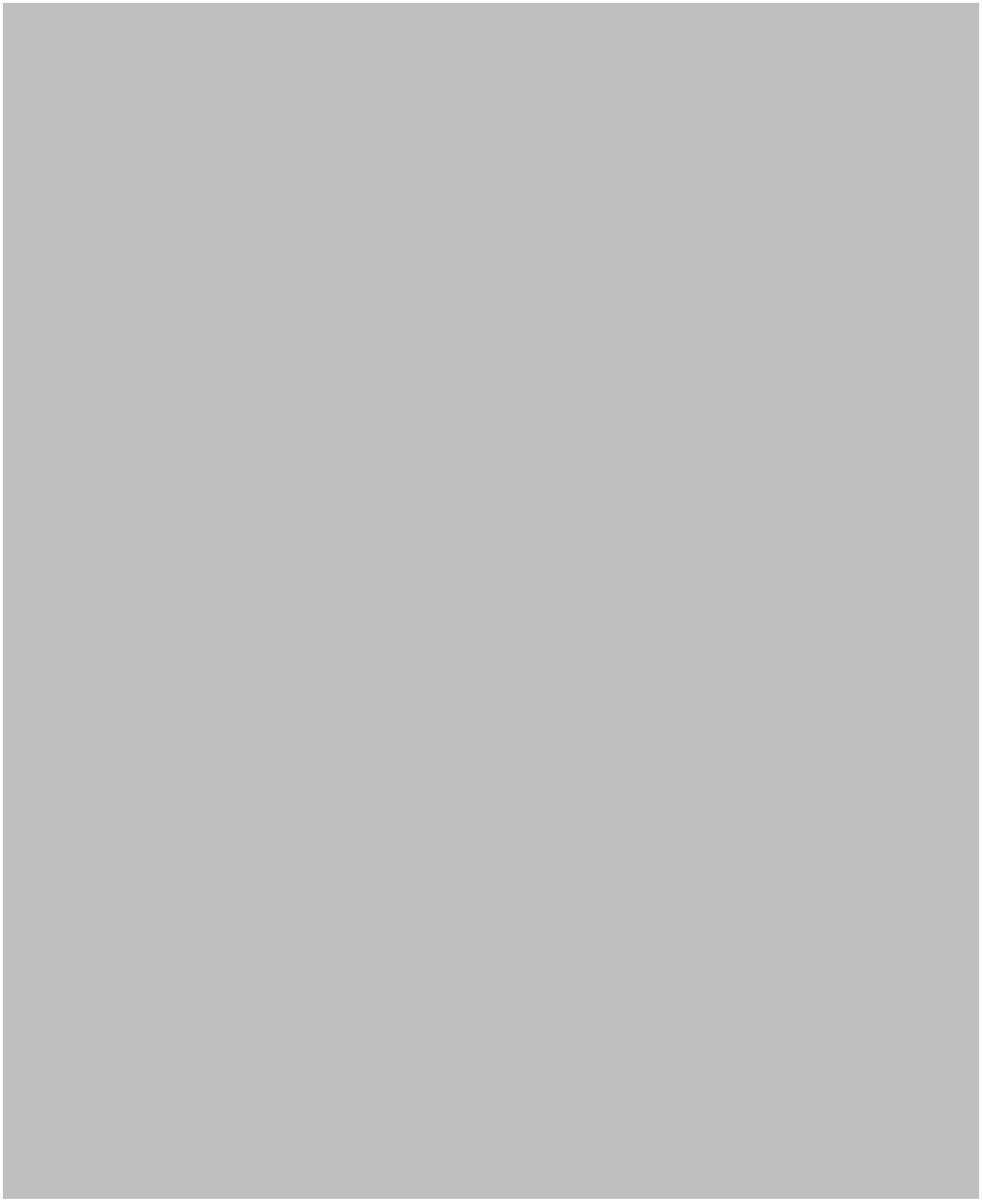


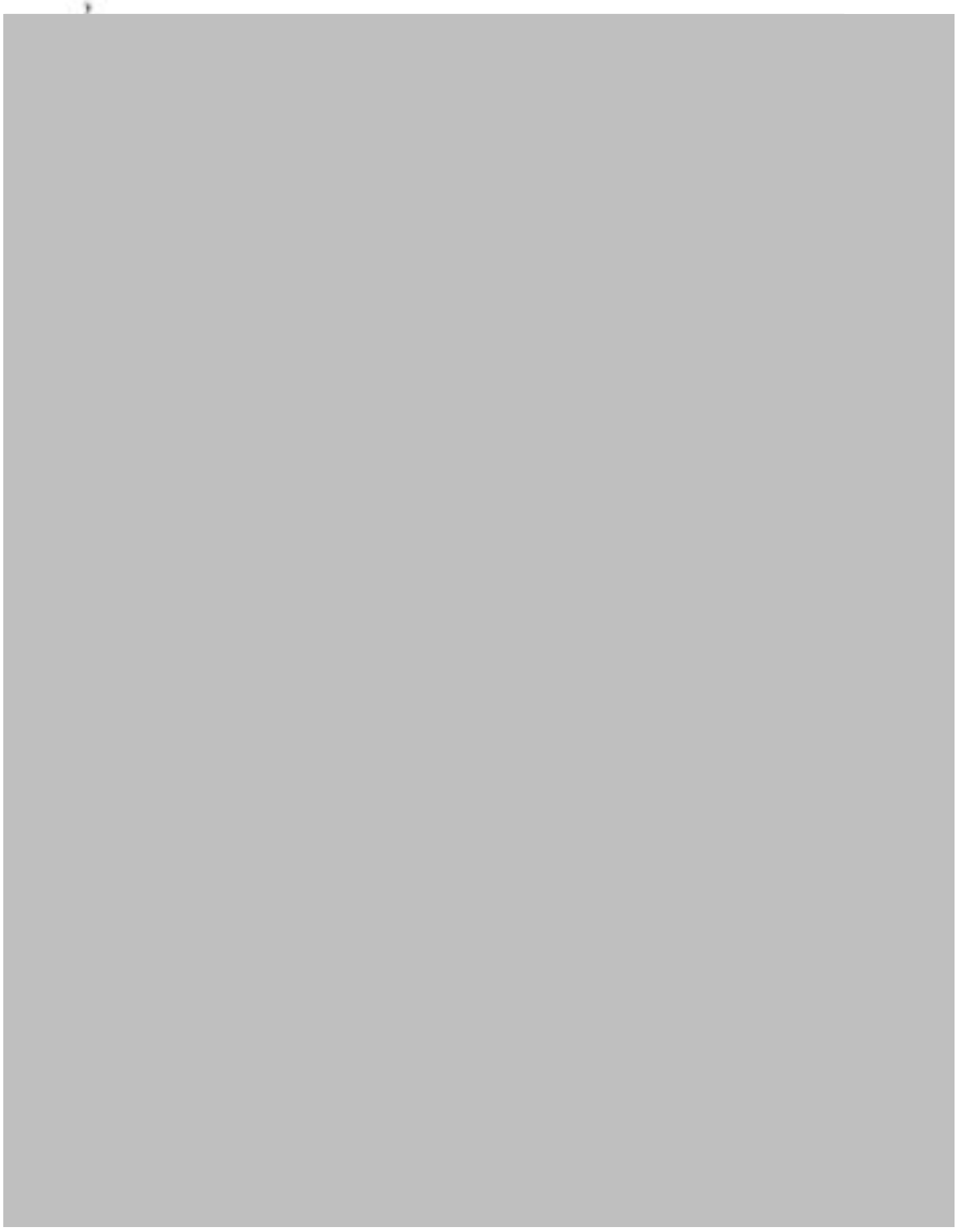


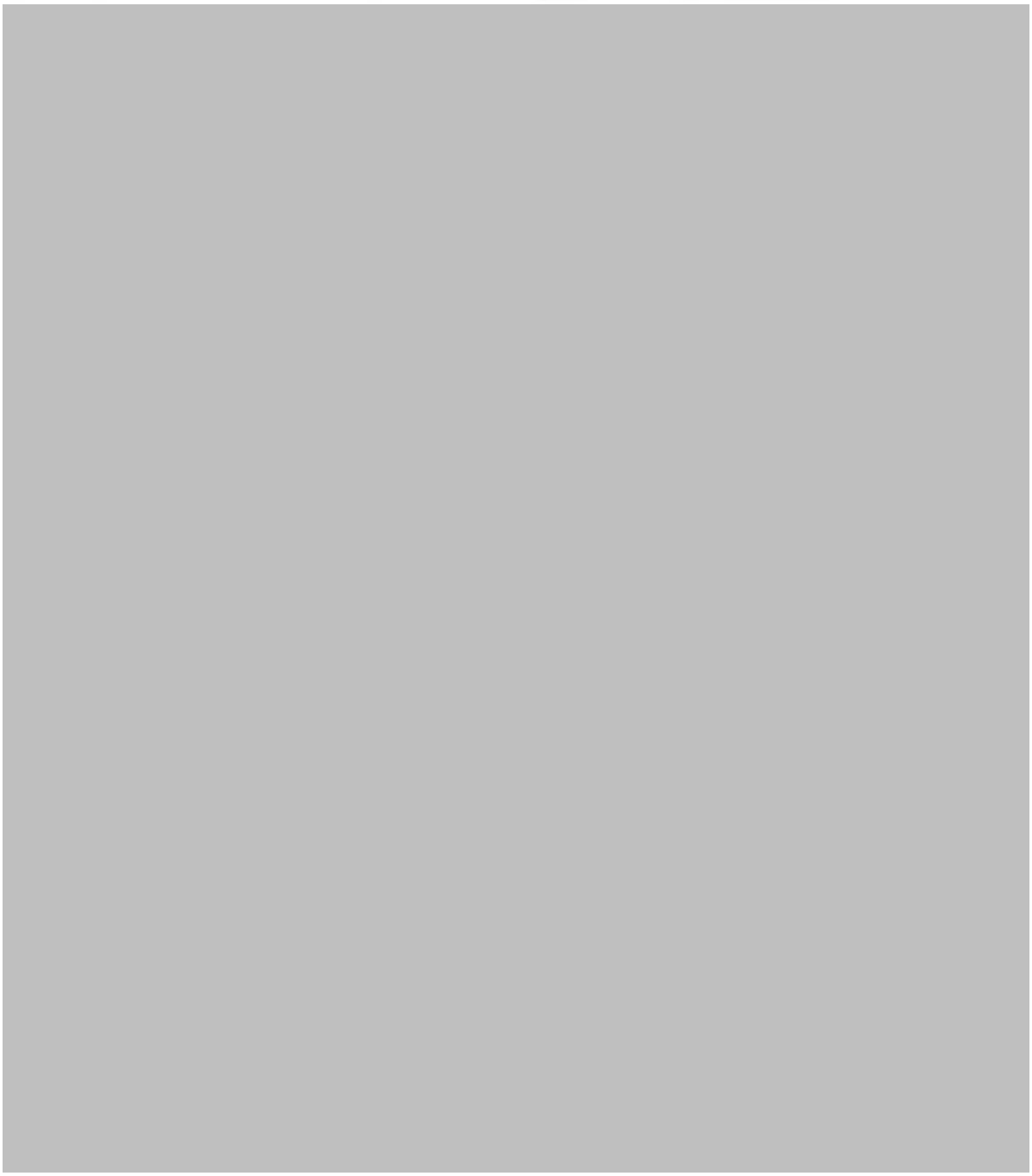


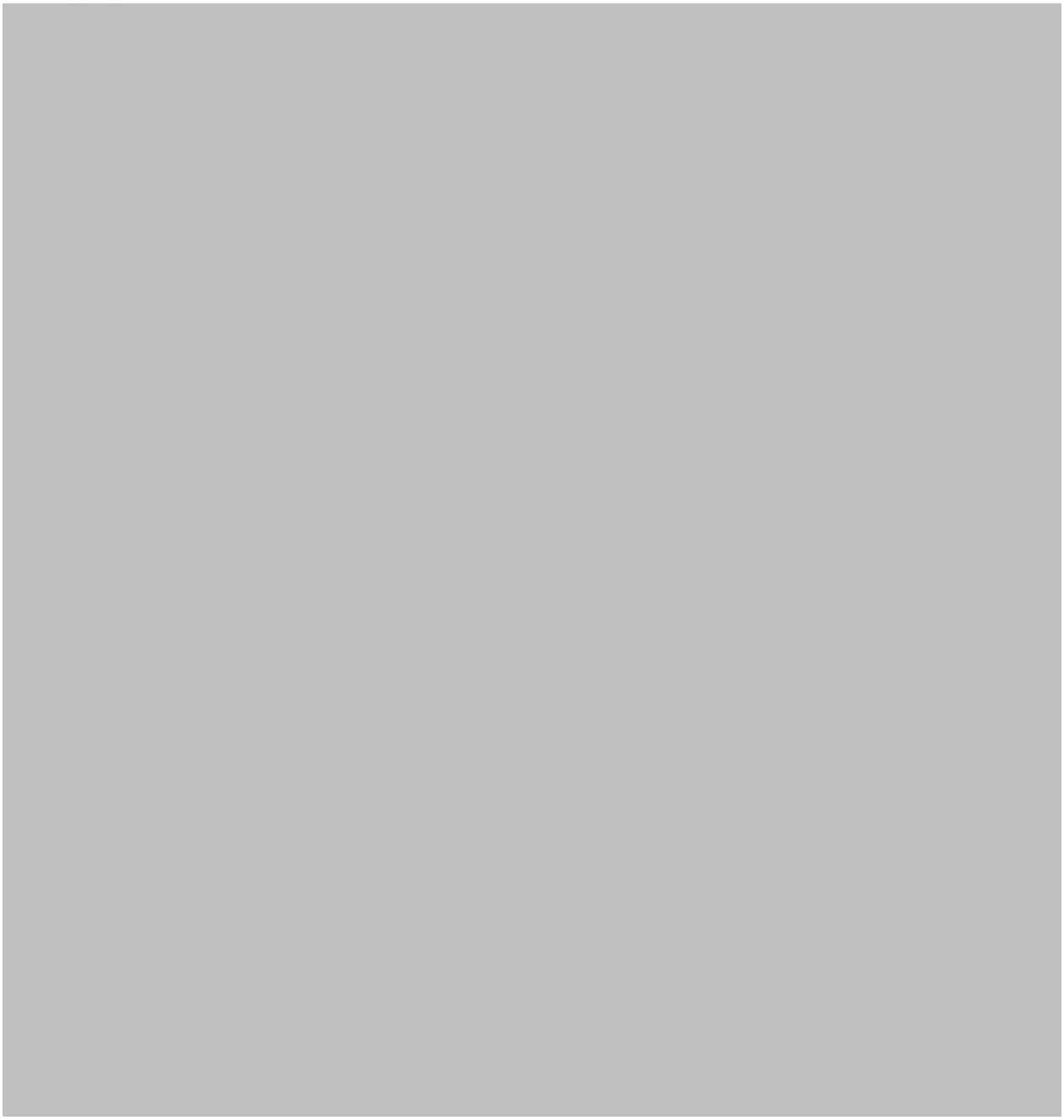


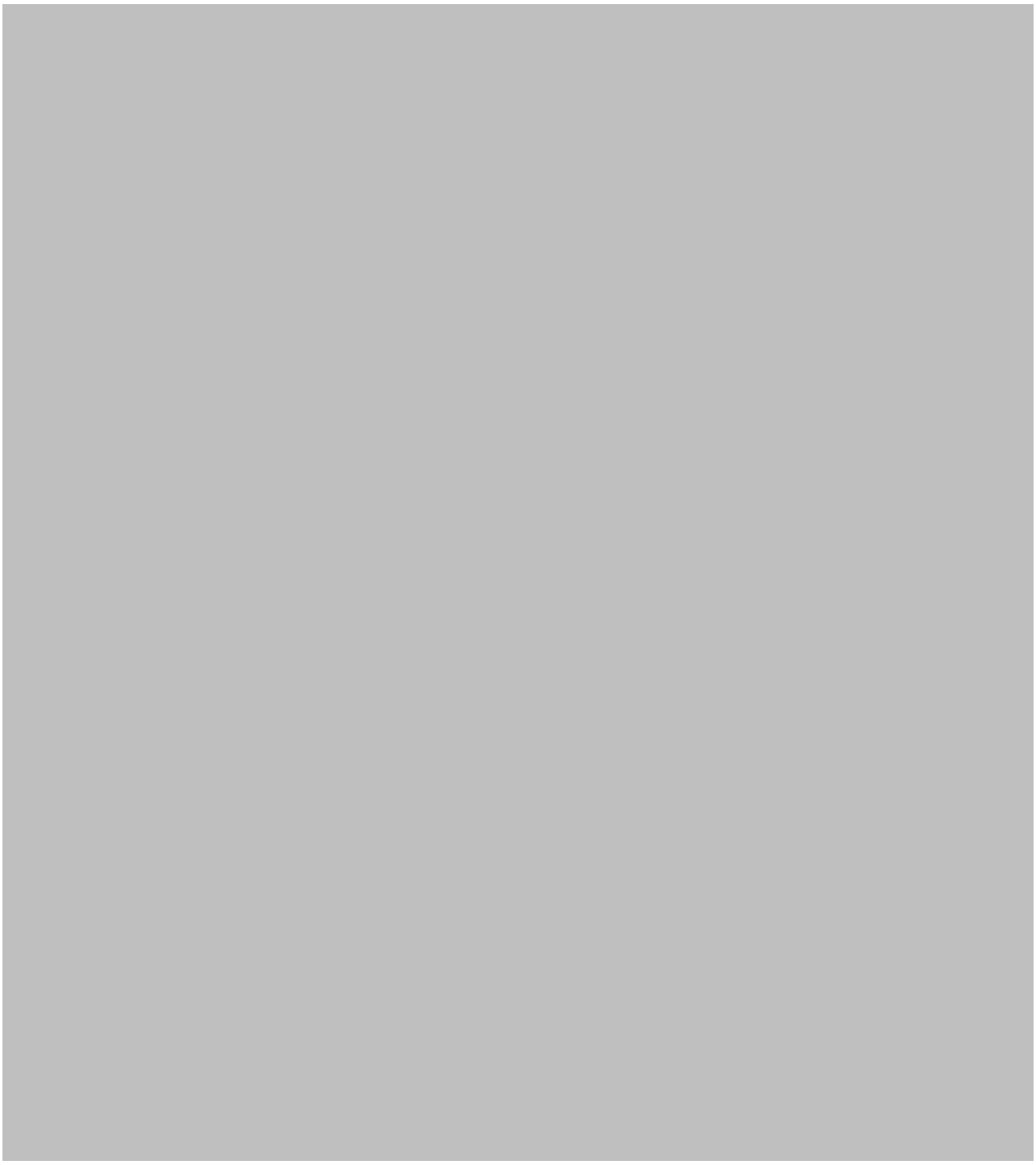


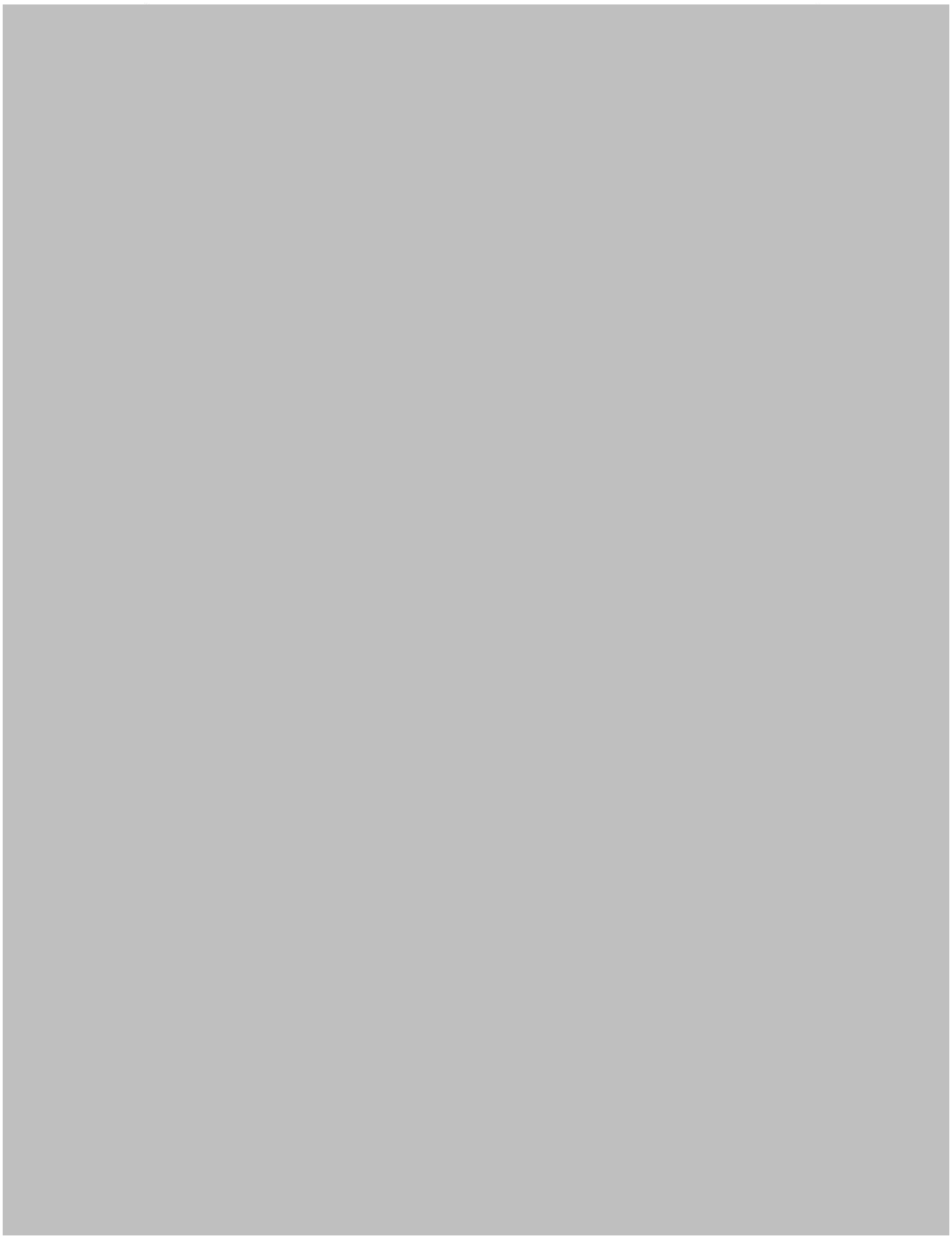


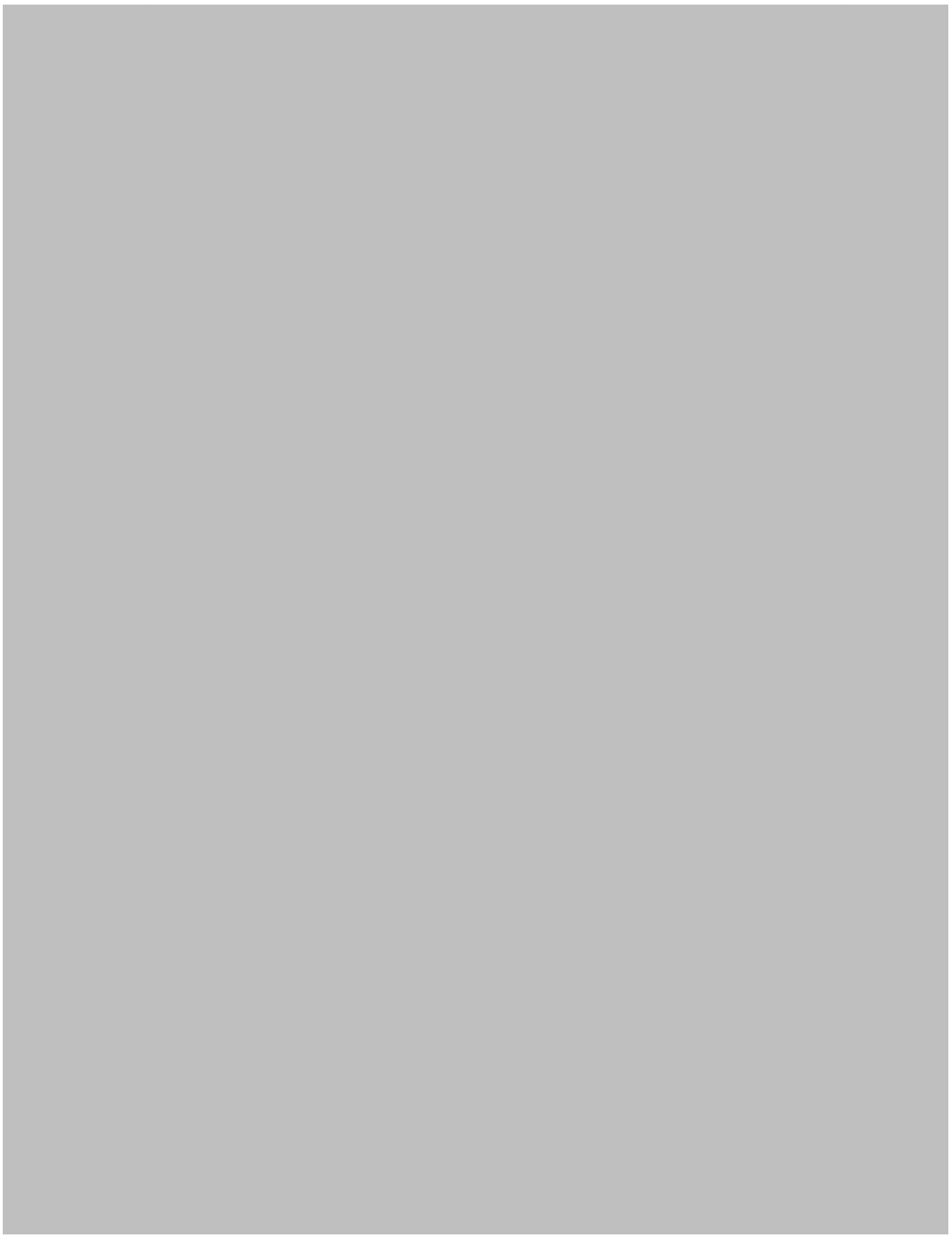


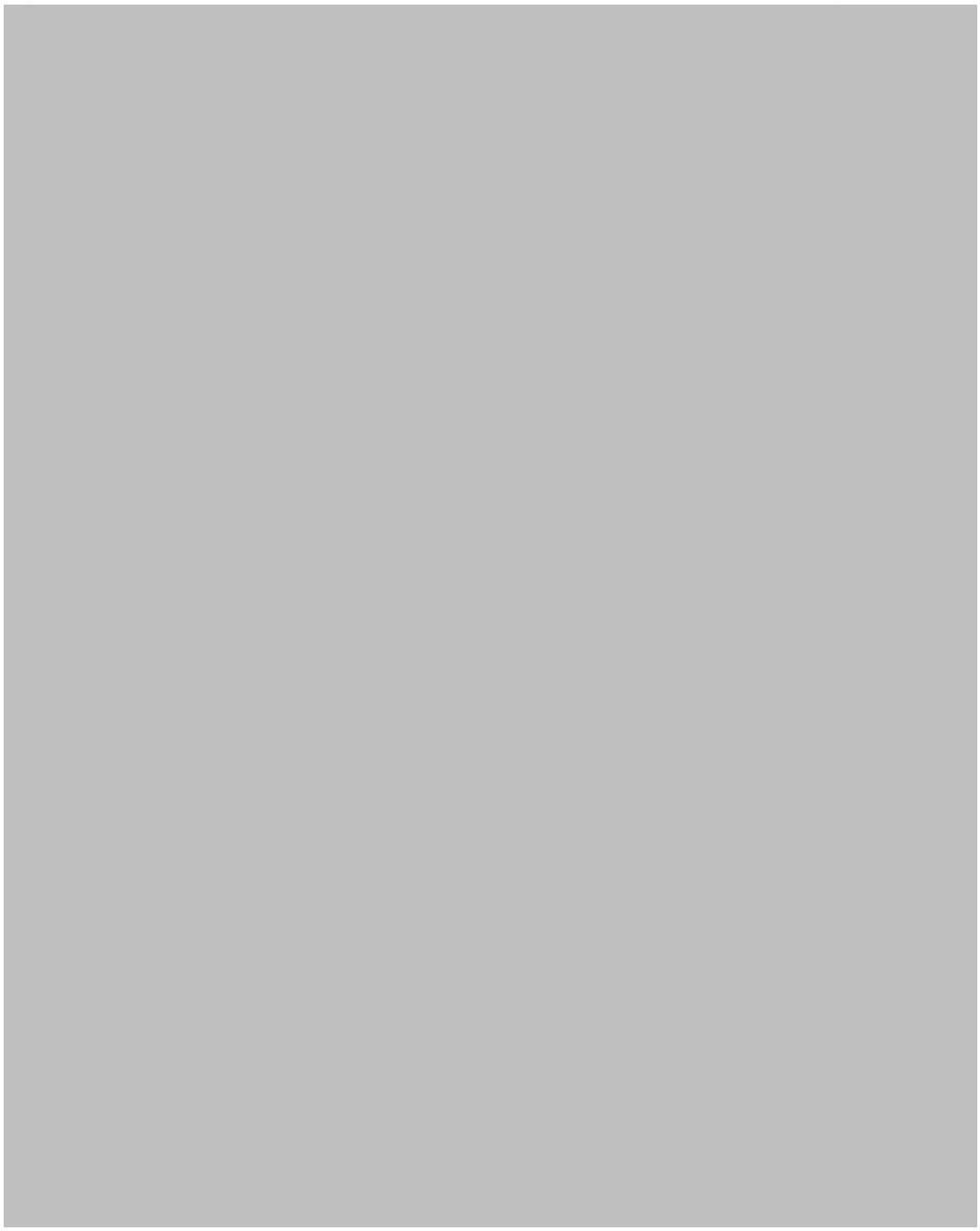


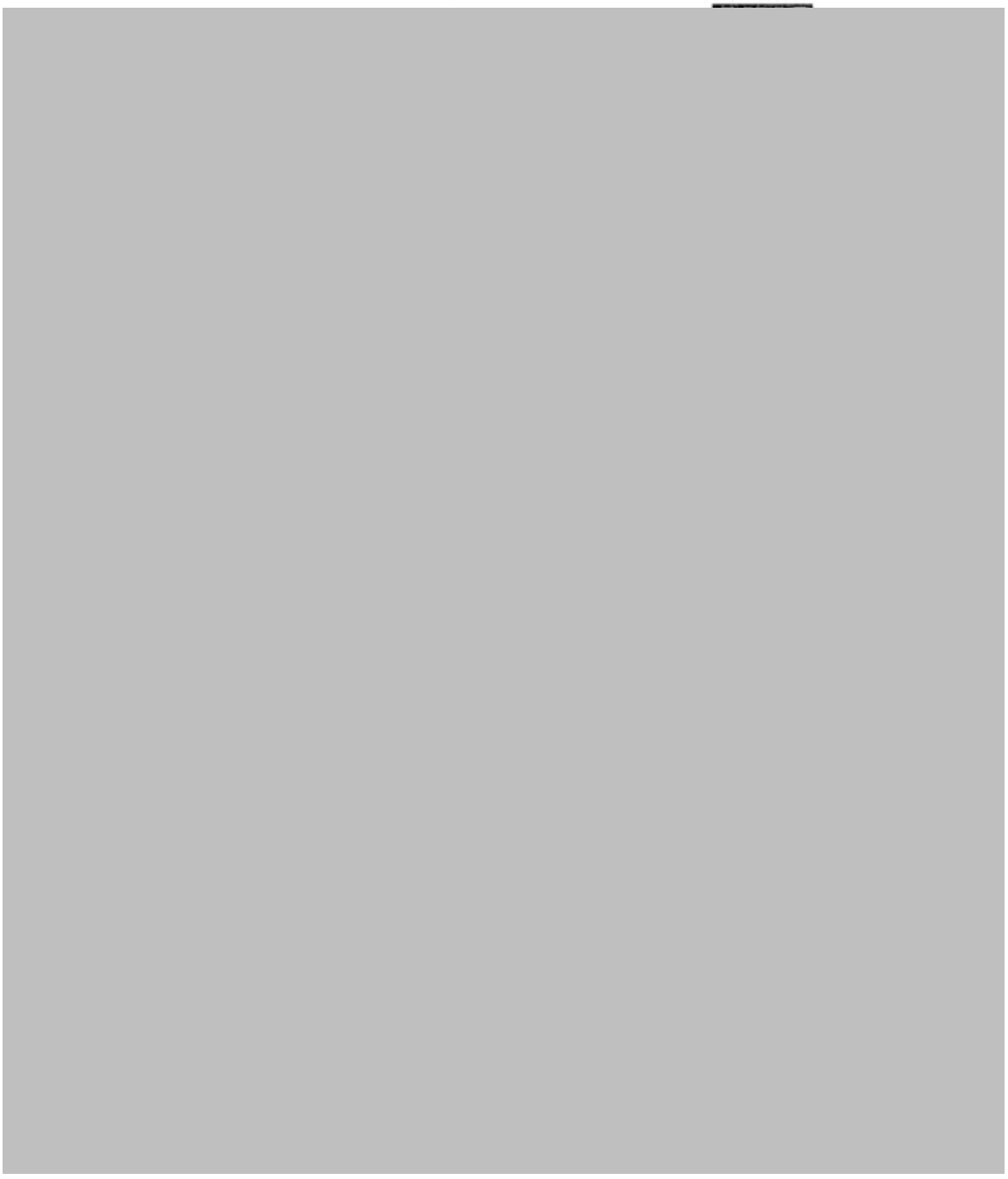


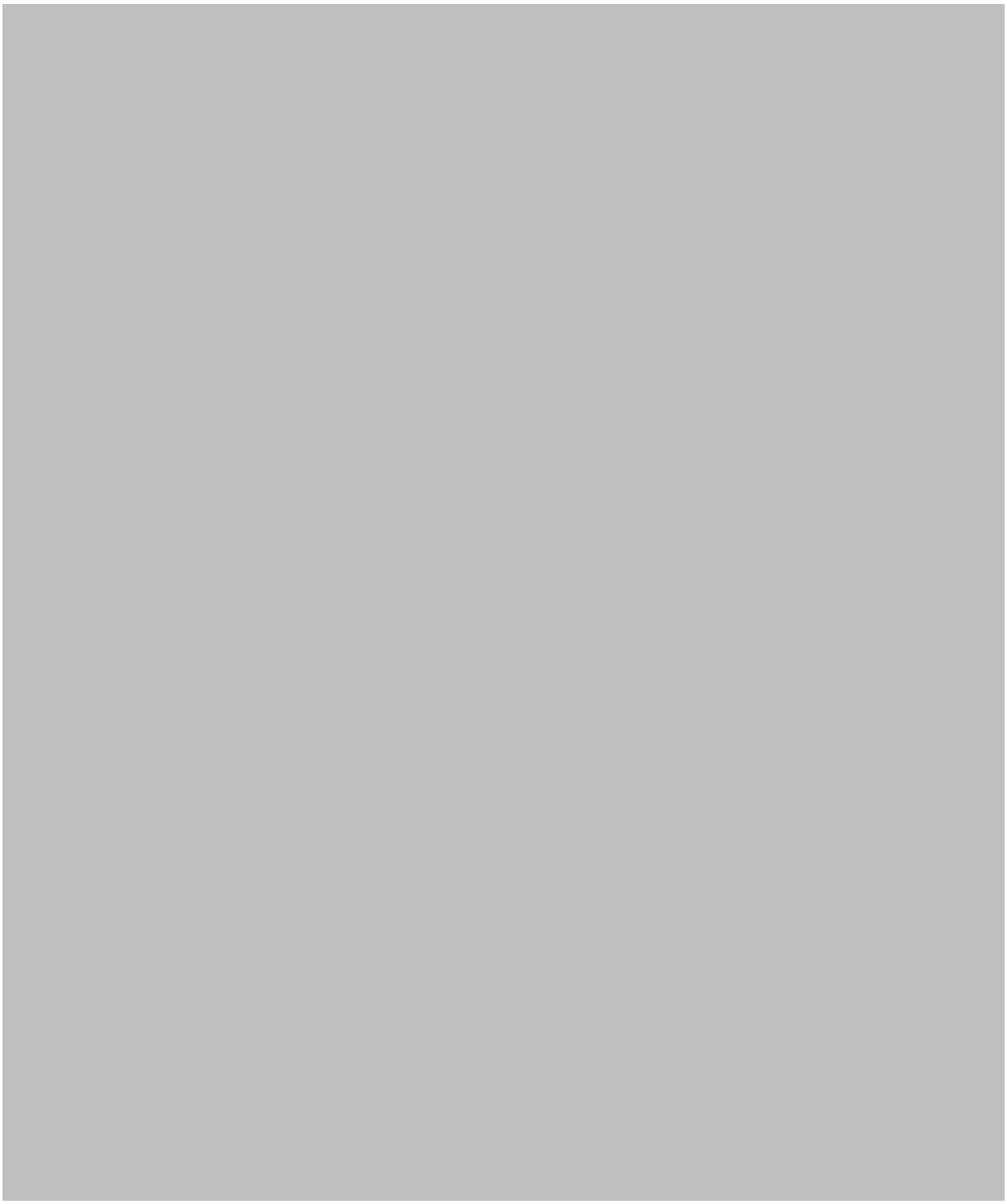


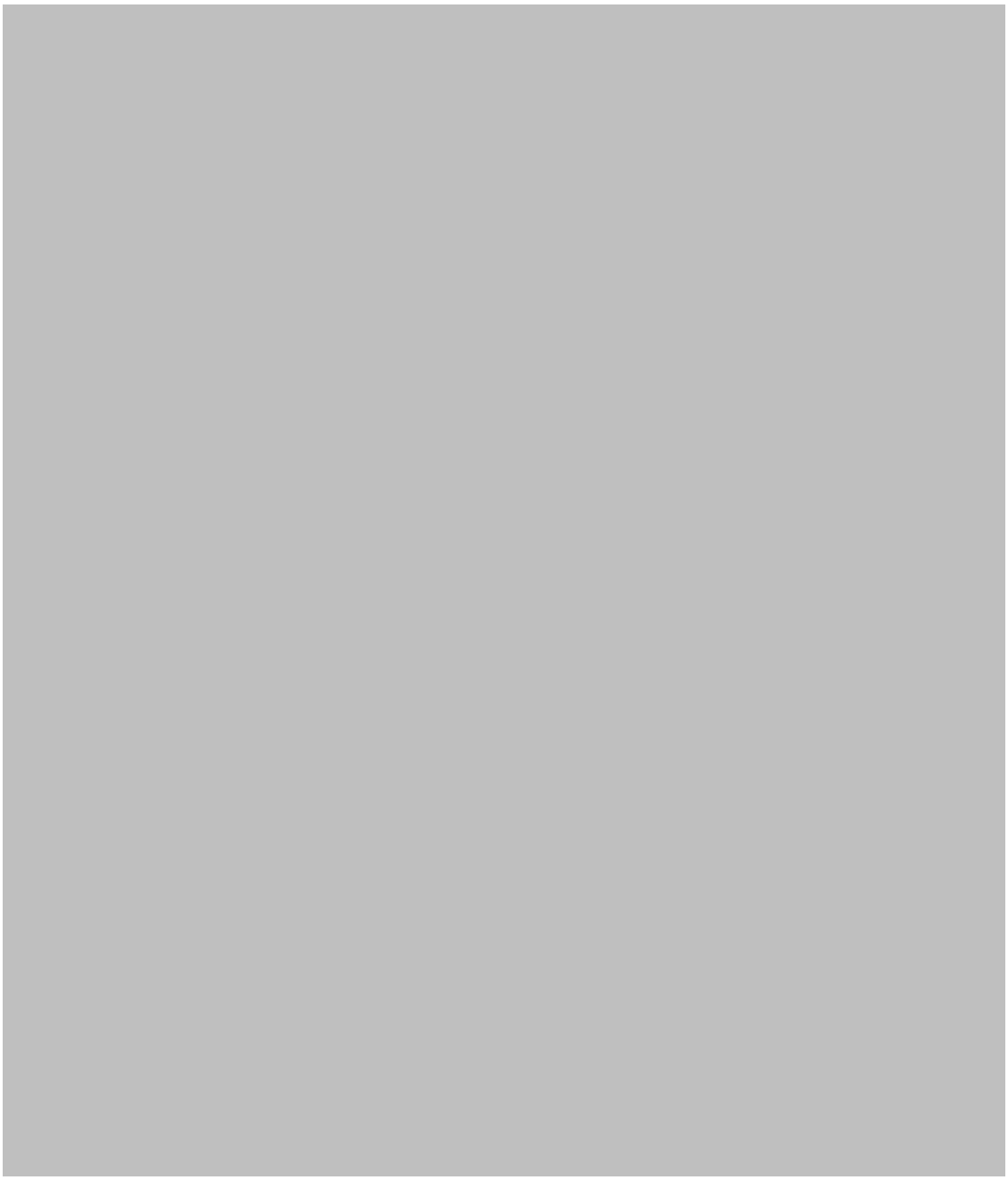


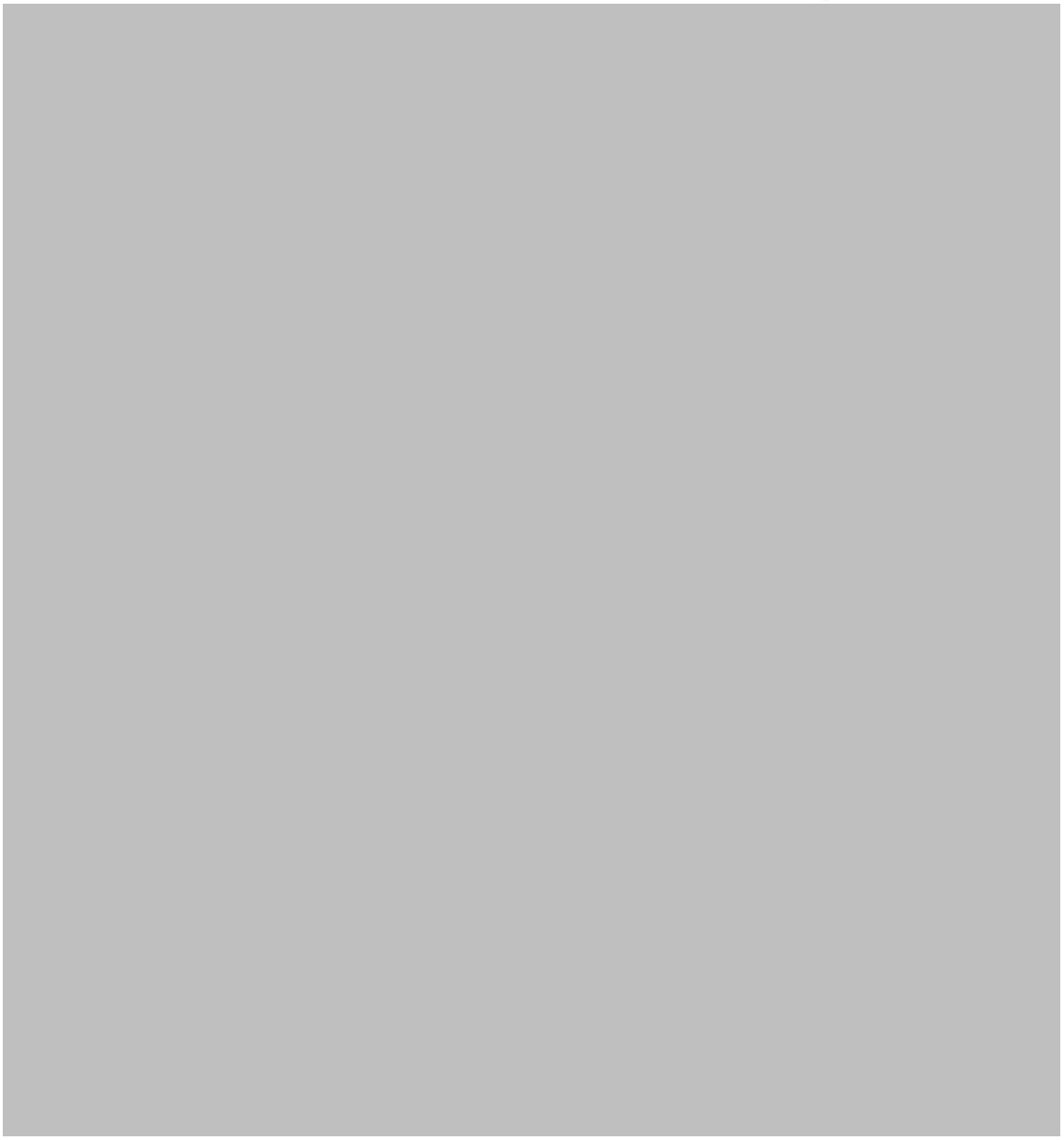


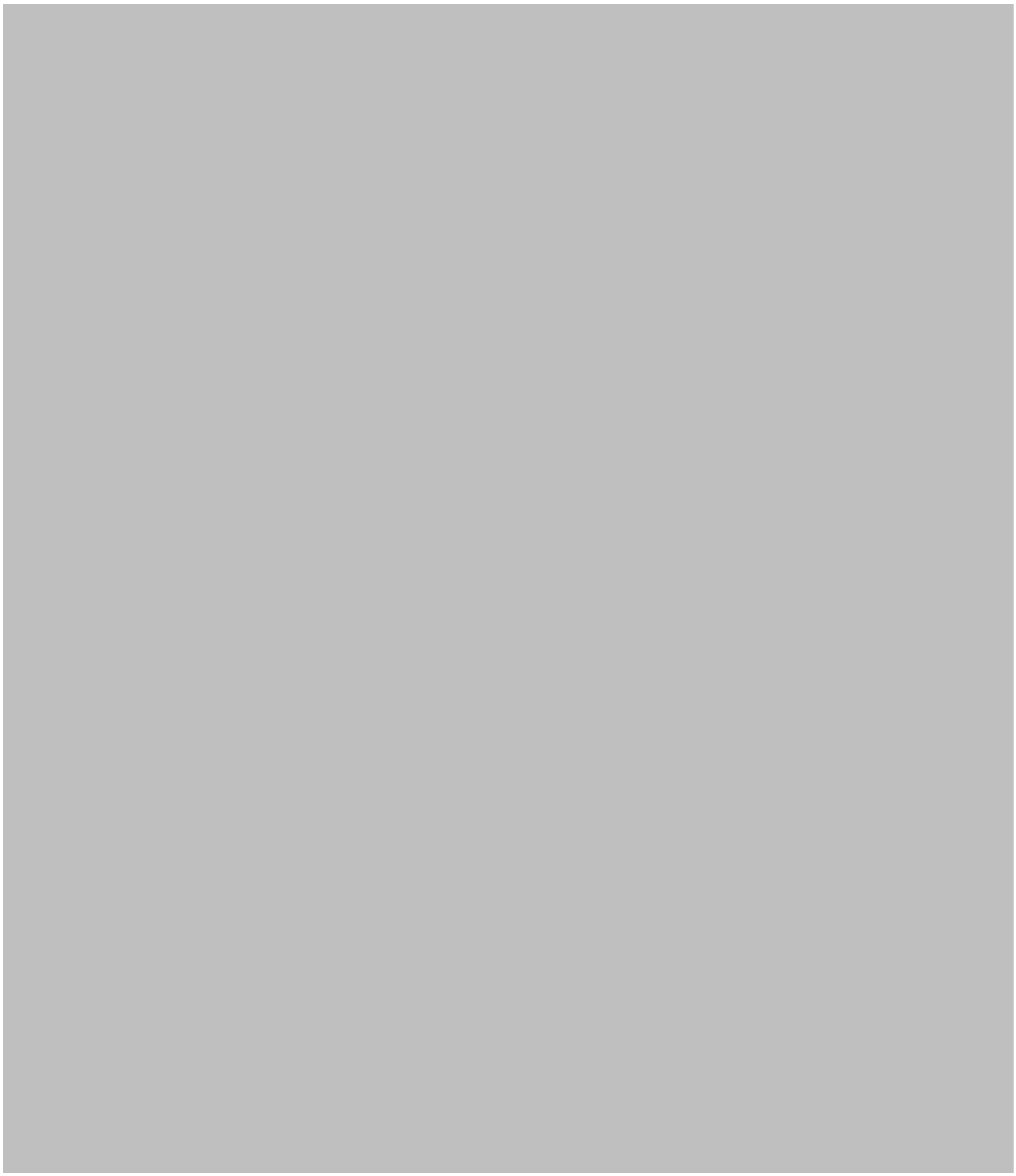


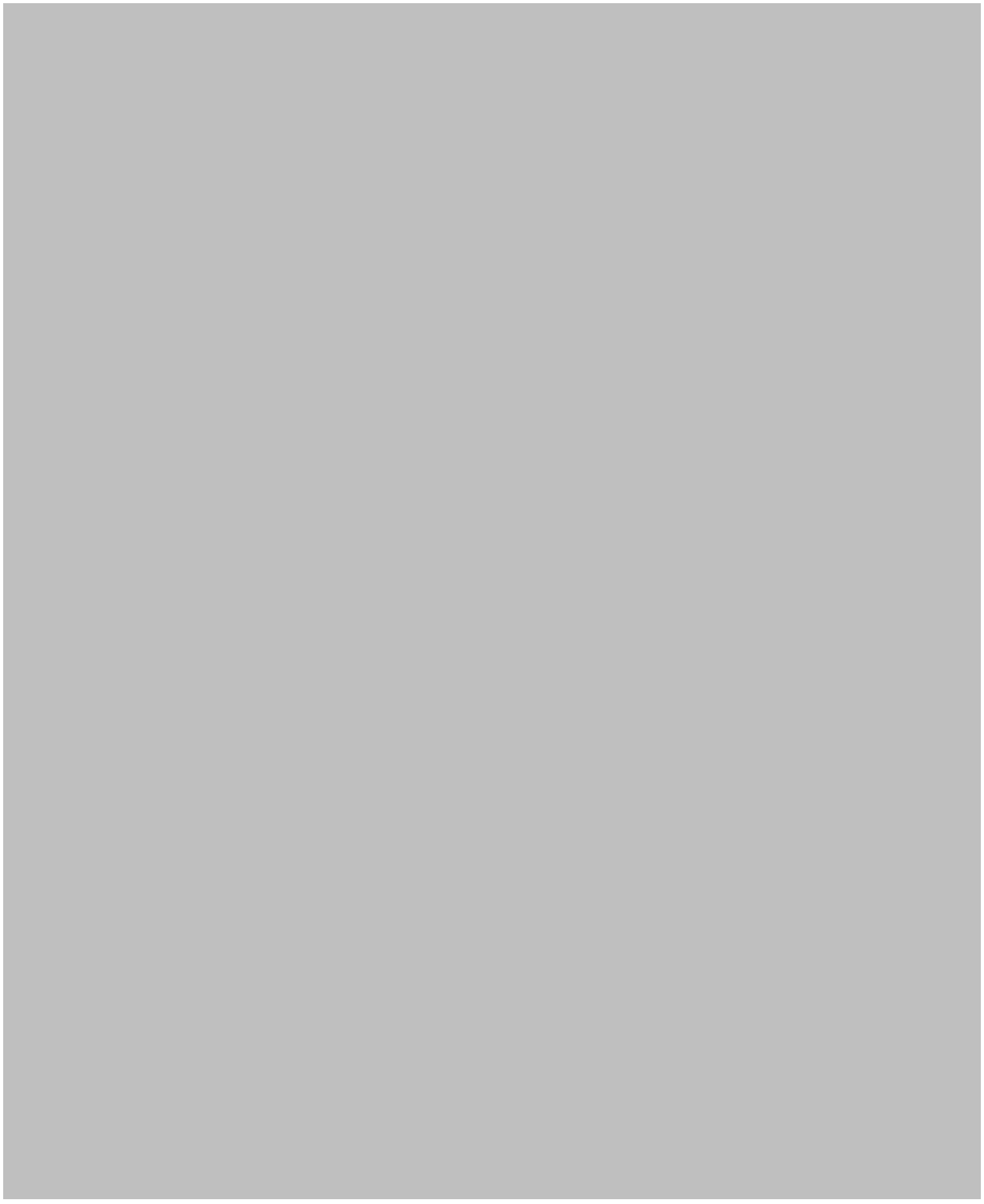


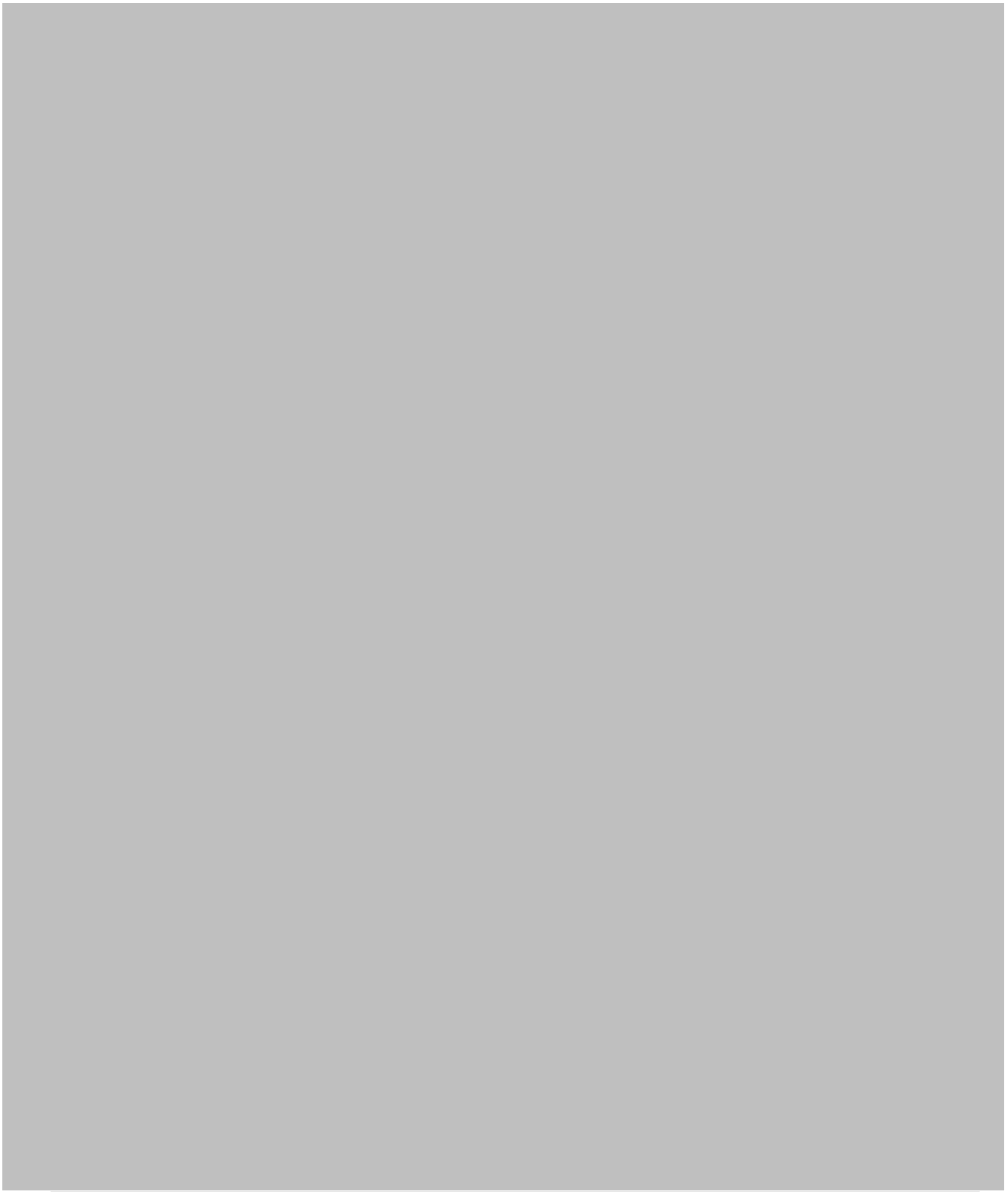


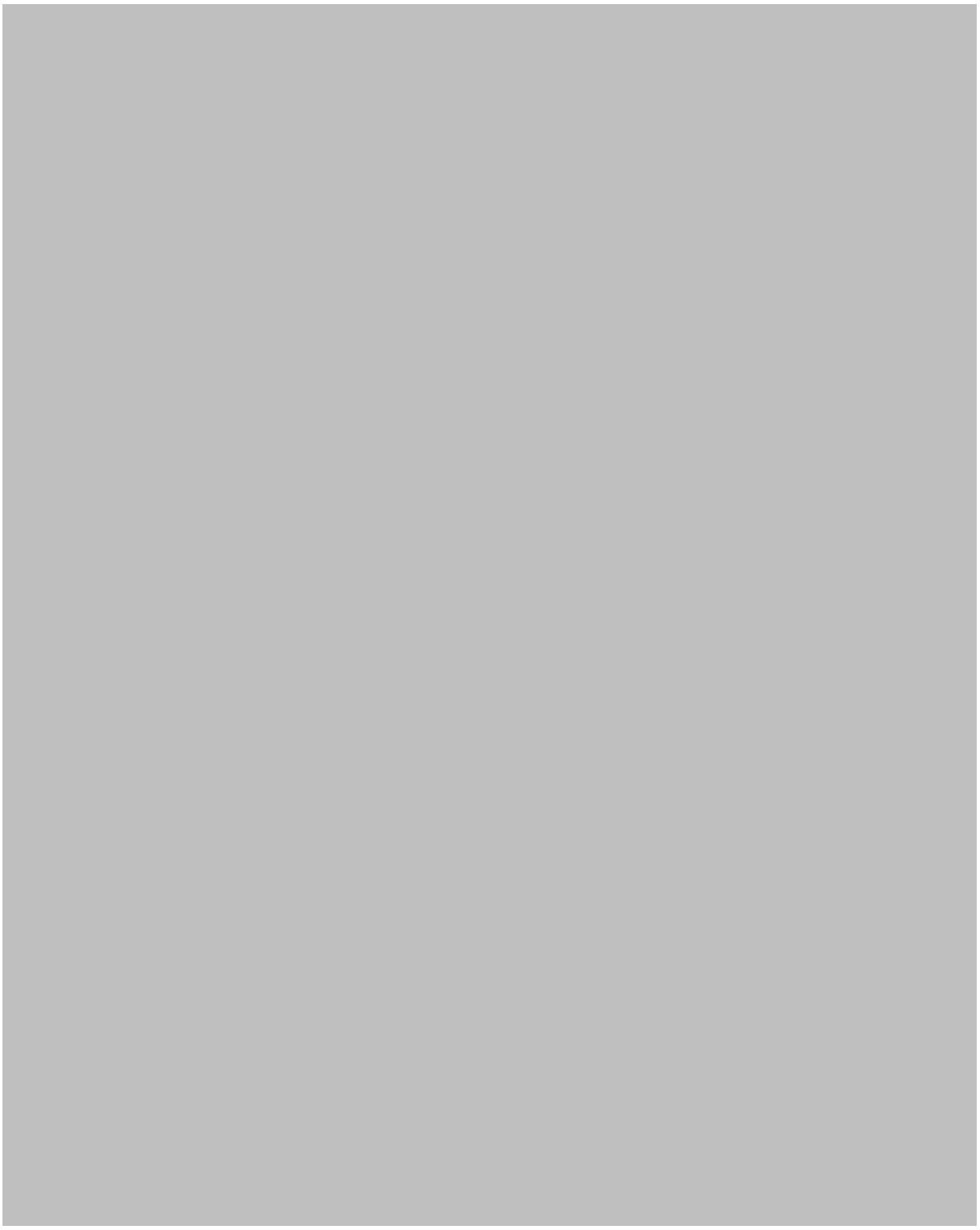


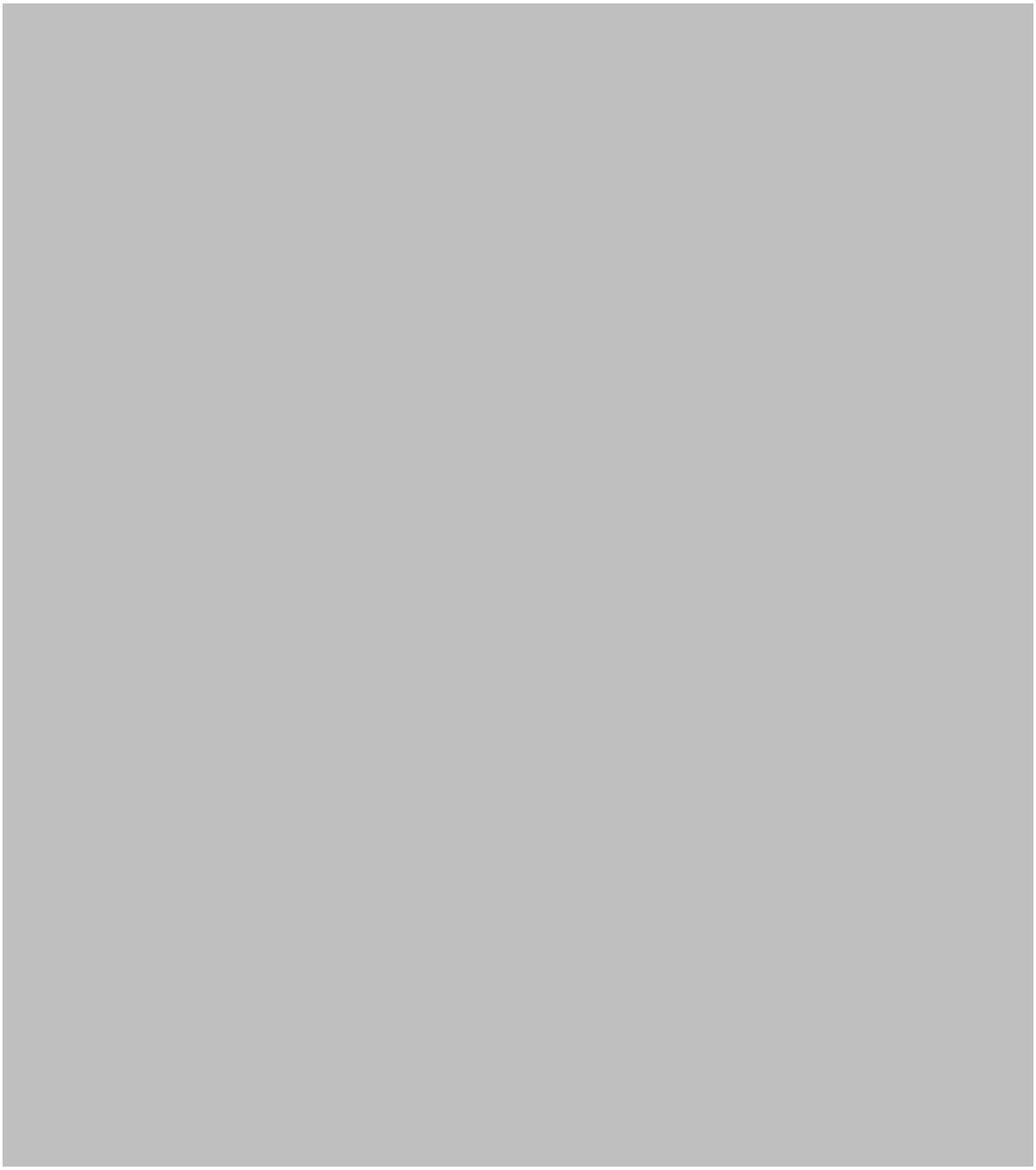


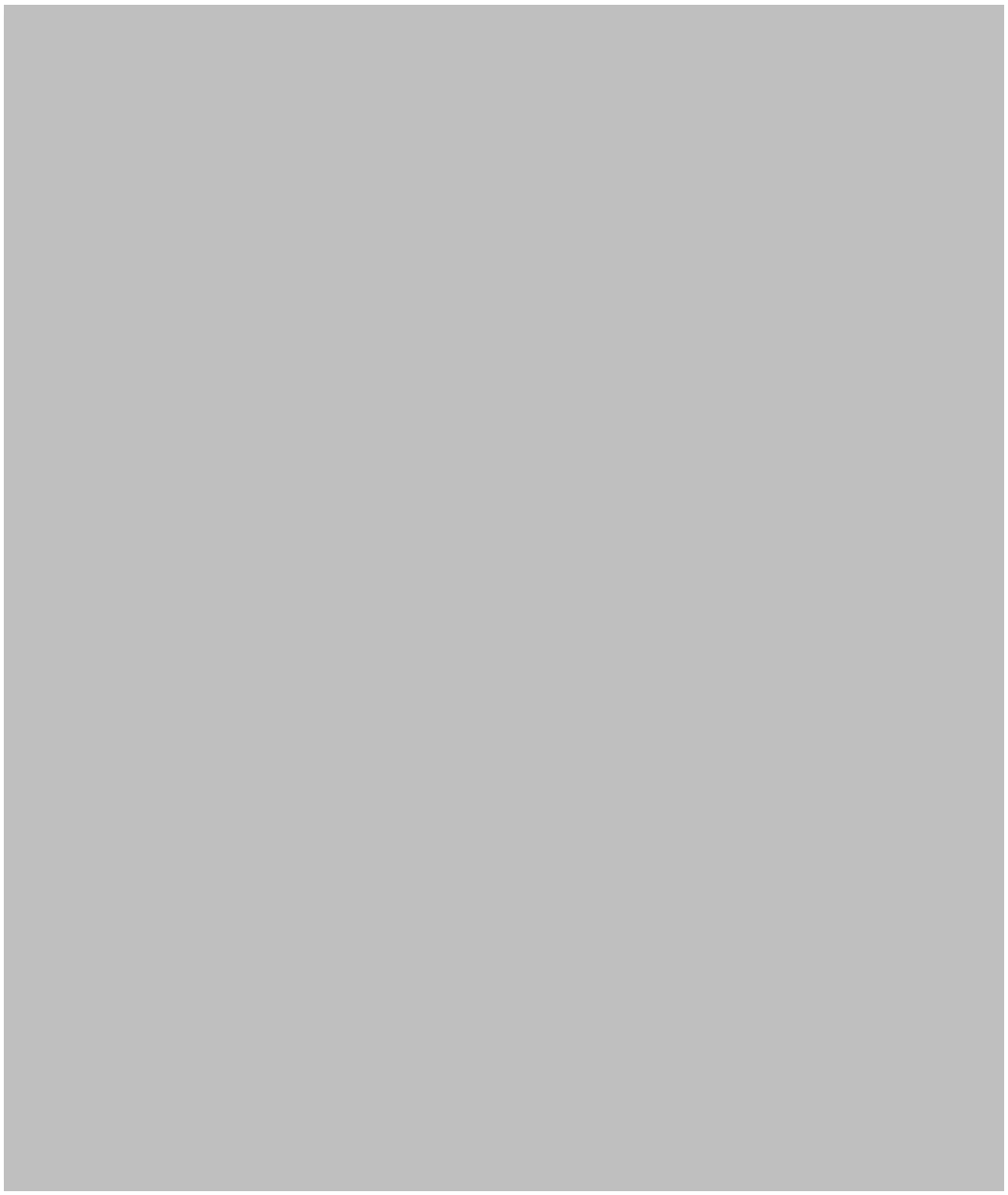


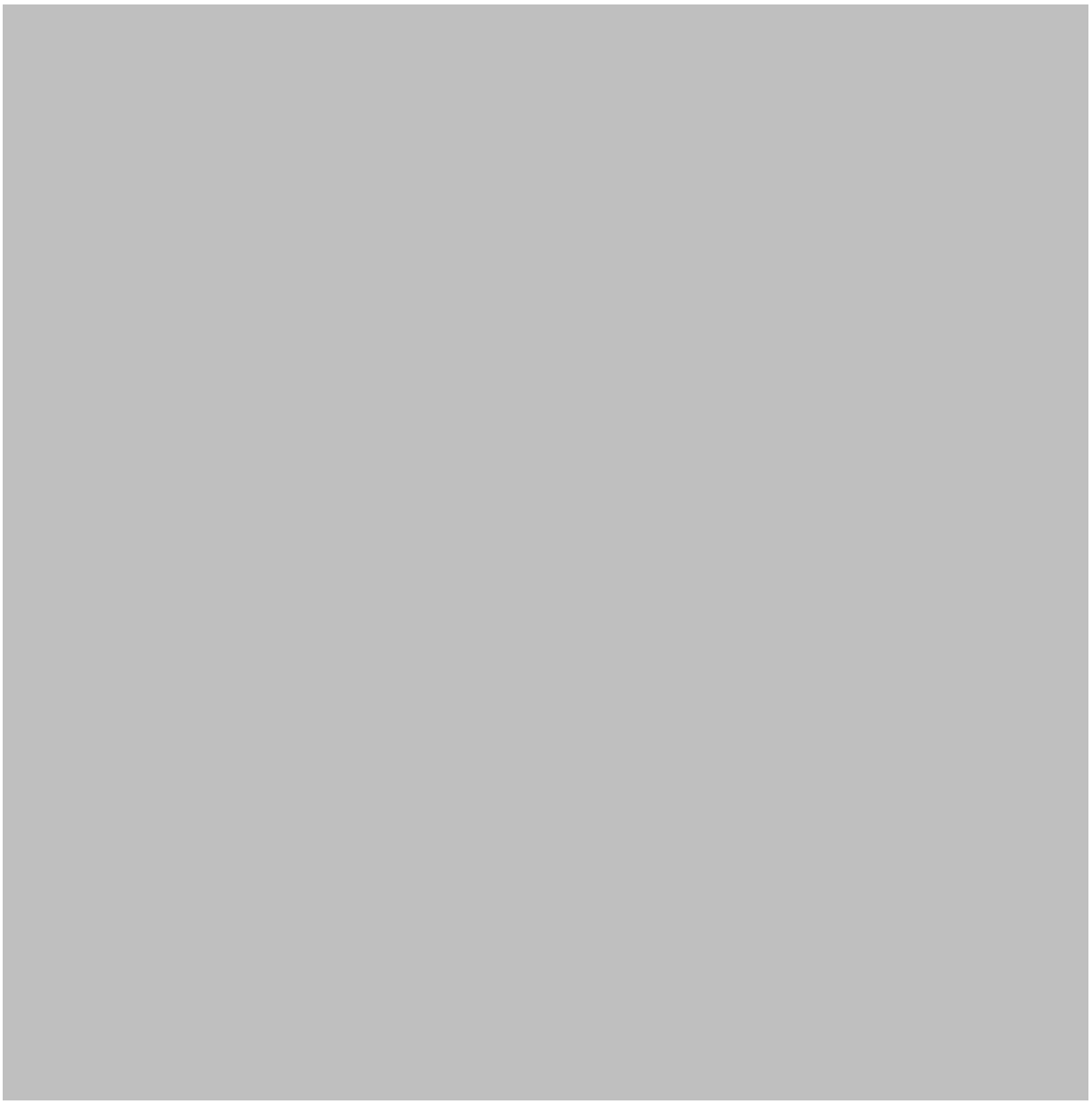


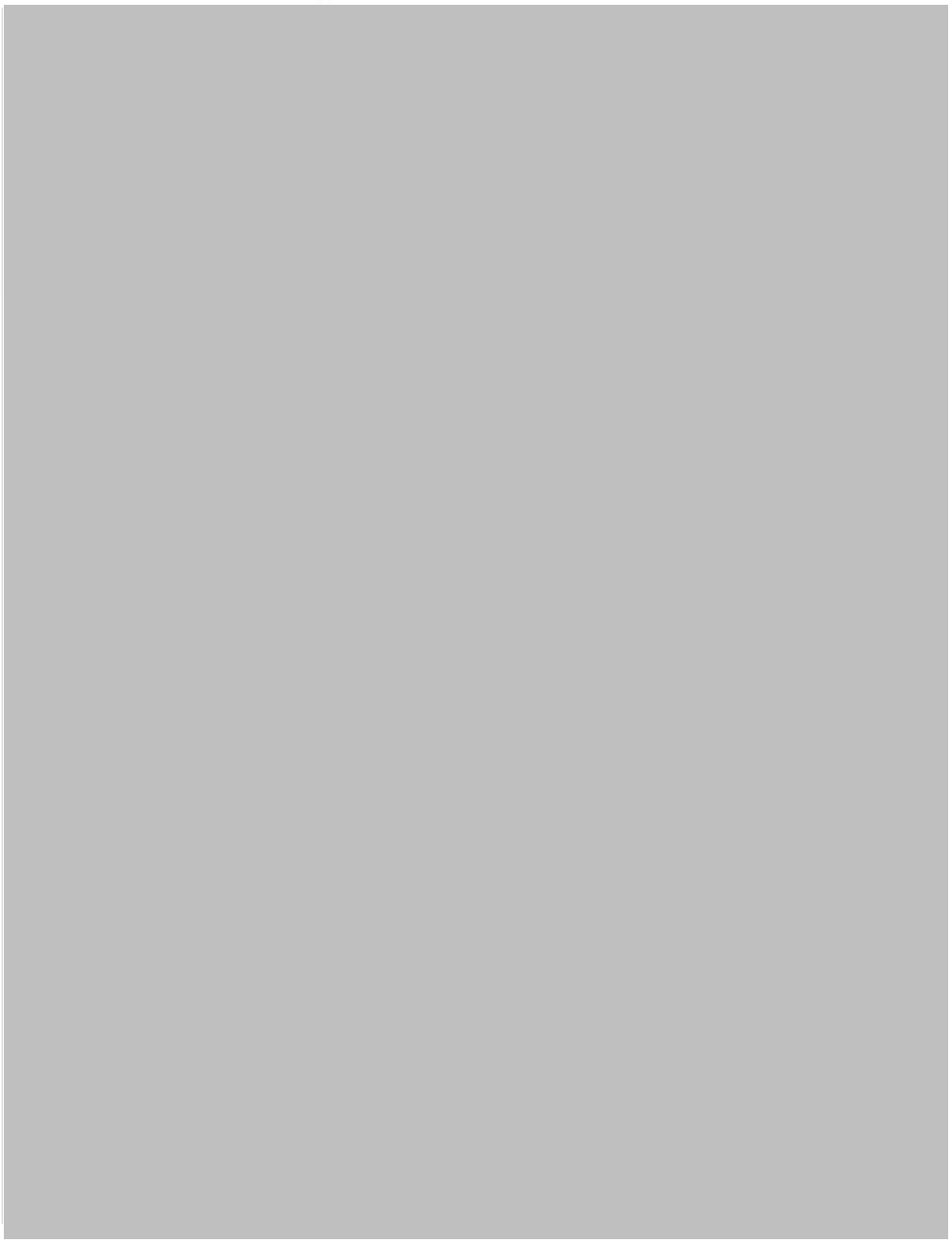


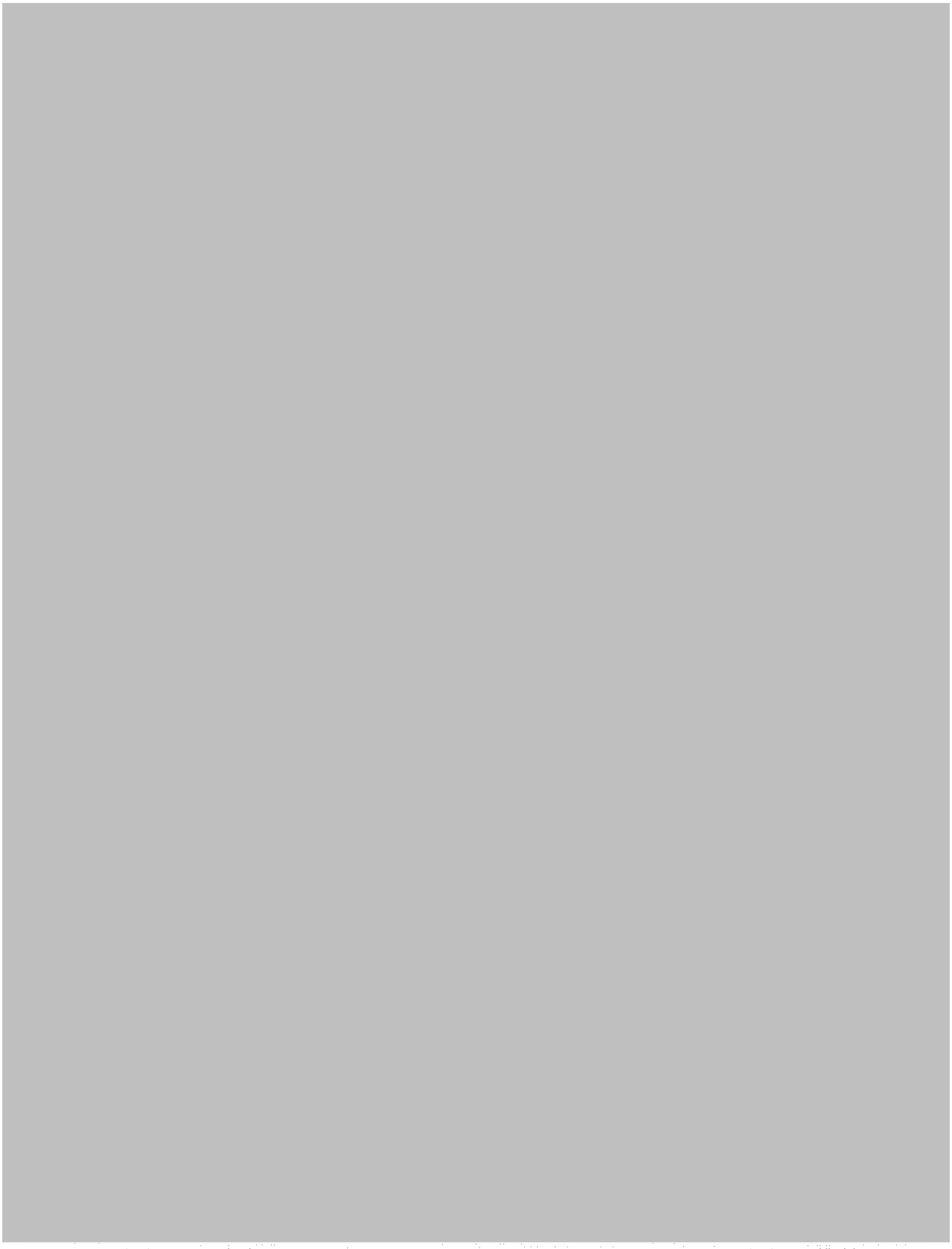


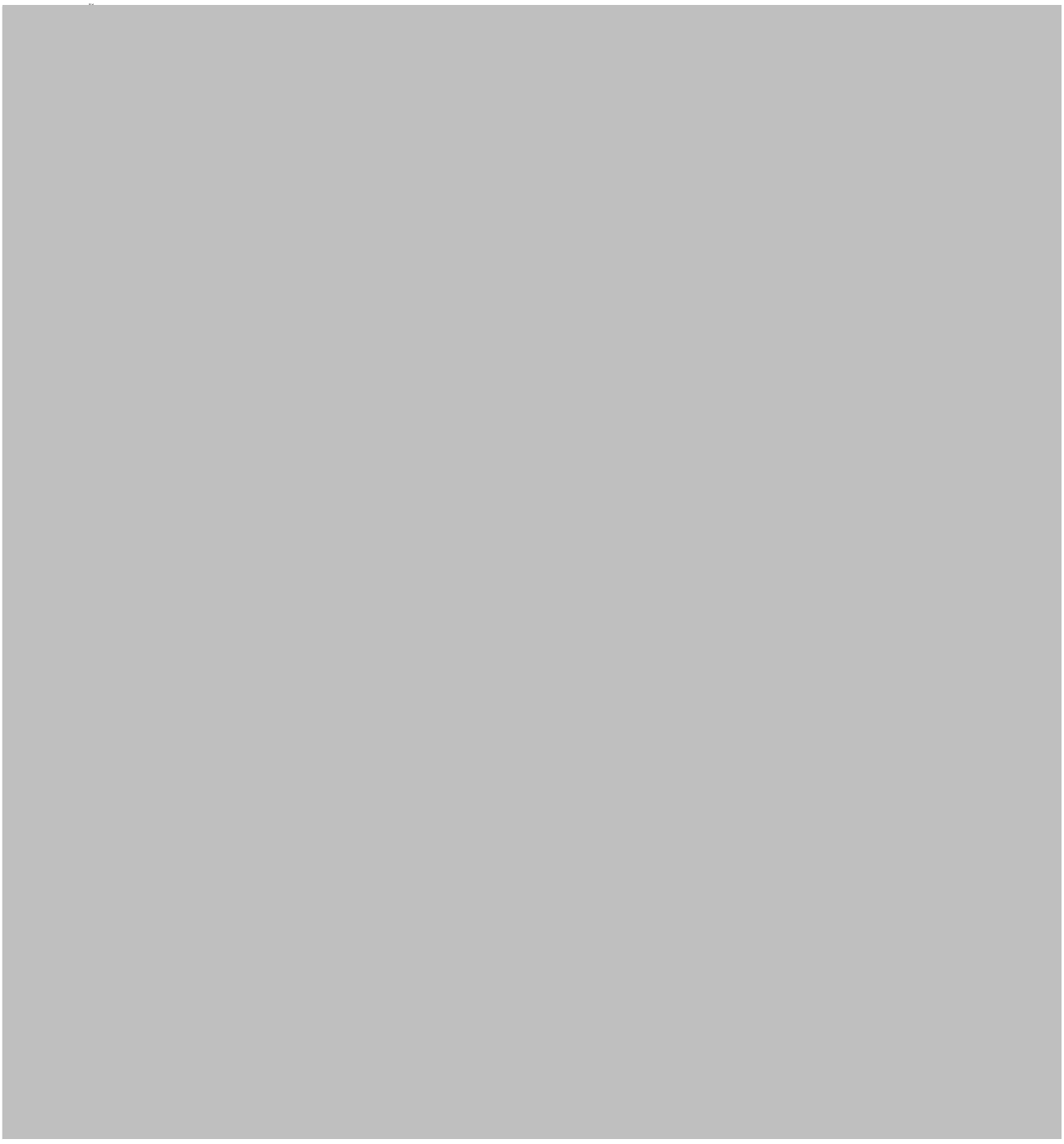


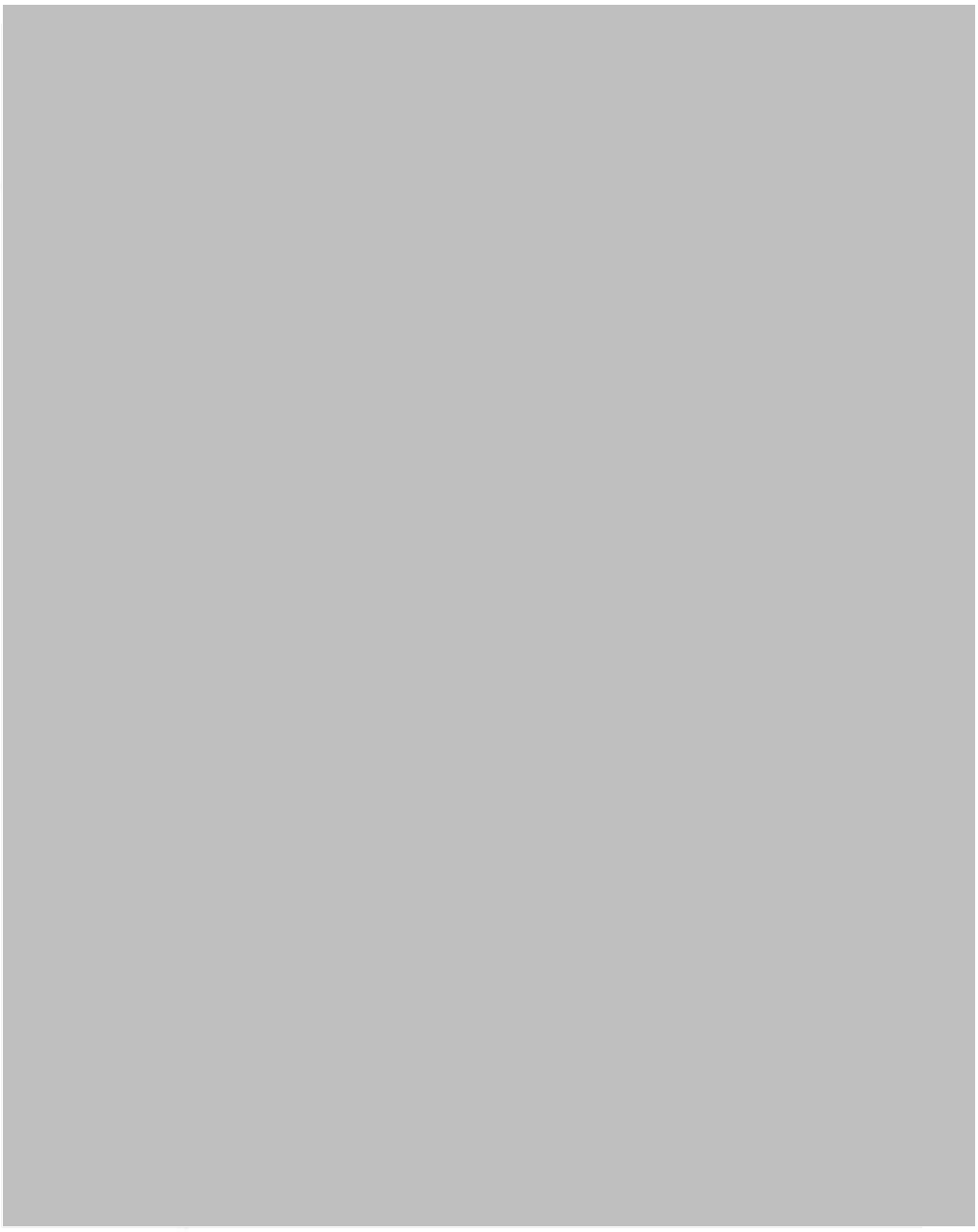


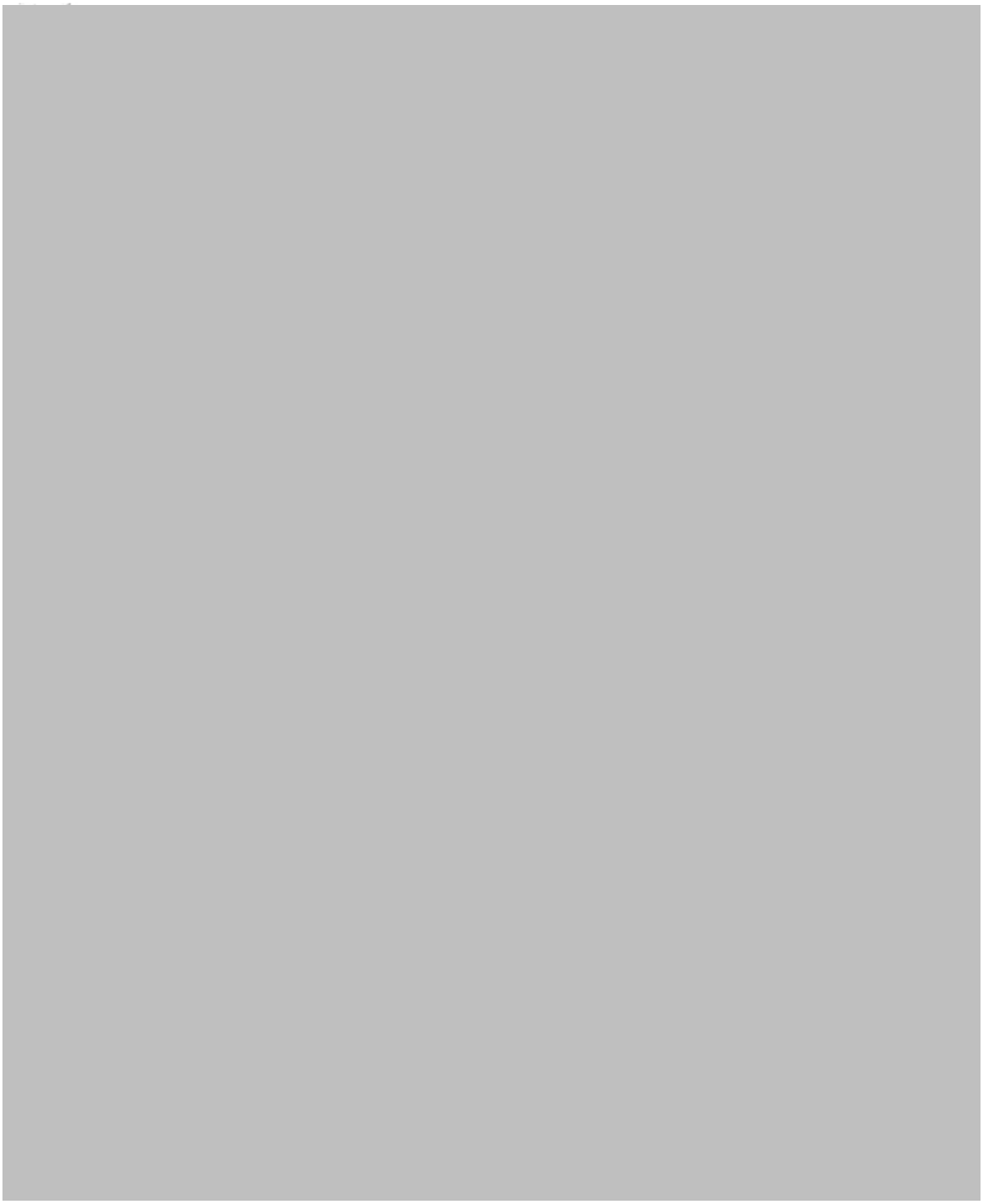


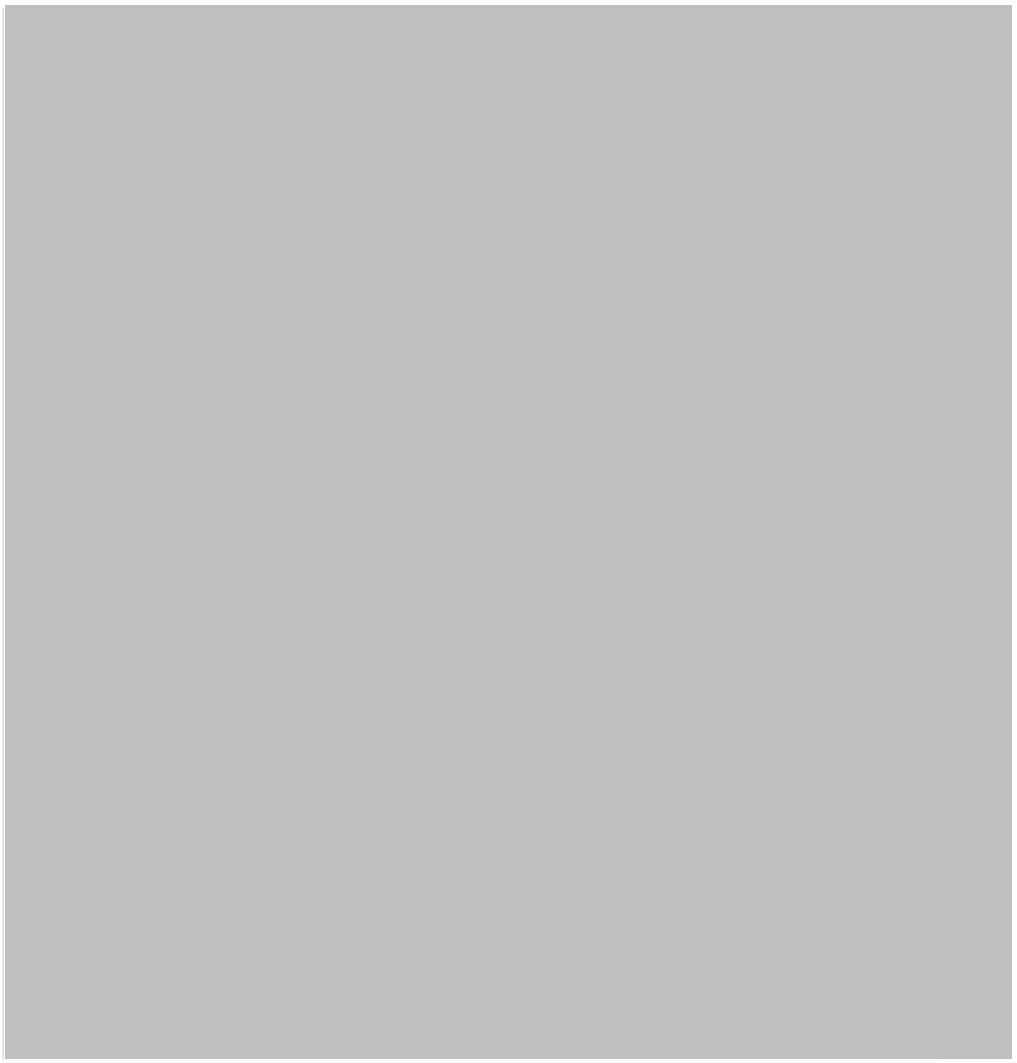












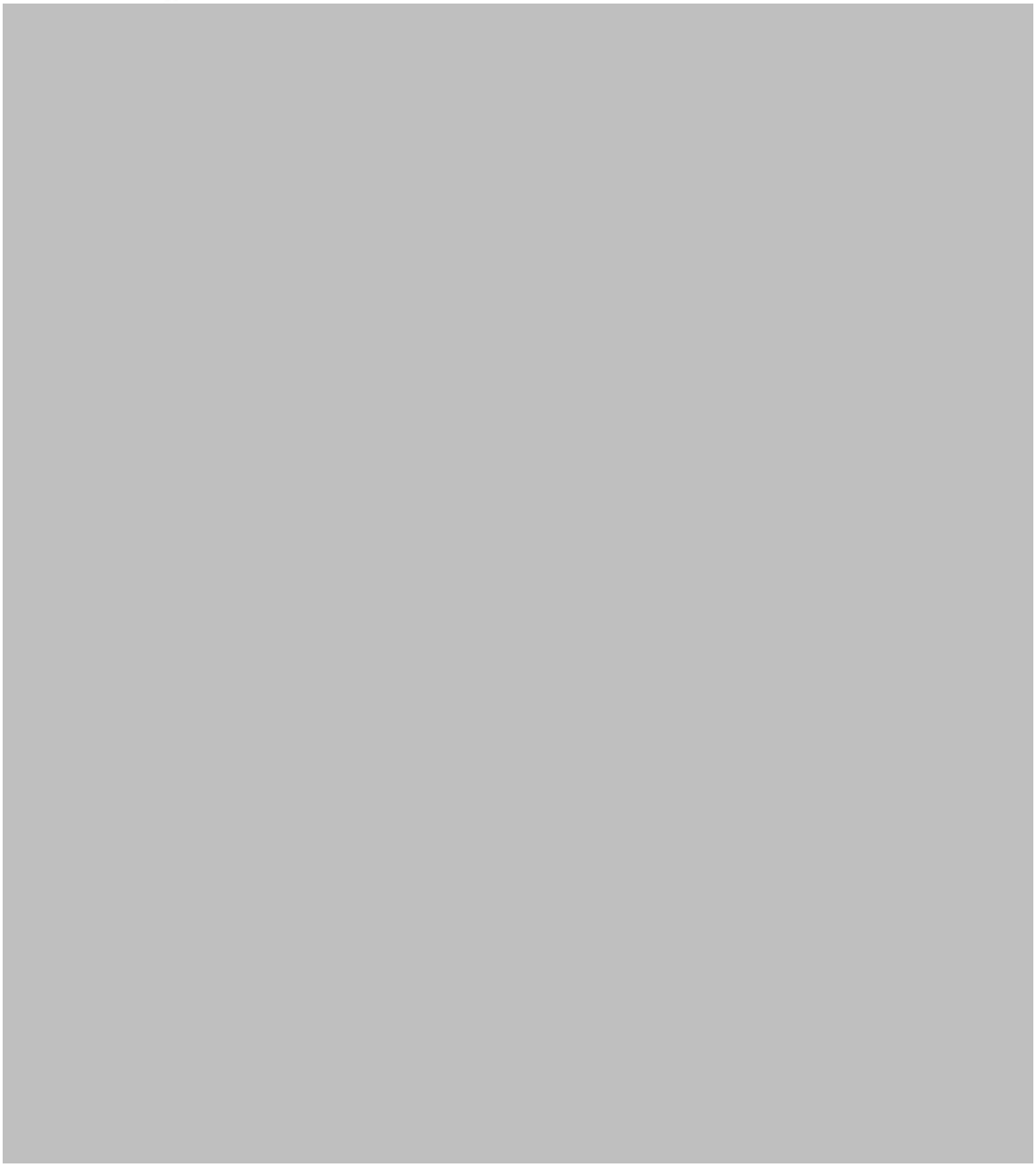
Appendix 2

- Template for intervention description and replication (TIDieR) checklist

Item	
Brief name	
1	Provide the name or a phrase that describes the intervention
Why	
2	Describe any rationale, theory, or goal of the elements essential to the intervention
What	
3	Materials: Describe any physical or informational materials used in the intervention, including those provided to participants or used in intervention delivery or in training of intervention providers. Provide information on where the materials can be accessed (such as online appendix, URL)
4	Procedures: Describe each of the procedures, activities, and/or processes used in the intervention, including any enabling or support activities
Who provided	
5	For each category of intervention provider (such as psychologist, nursing assistant), describe their expertise, background, and any specific training given
How	
6	Describe the modes of delivery (such as face to face or by some other mechanism, such as internet or telephone) of the intervention and whether it was provided individually or in a group
Where	
7	Describe the type(s) of location(s) where the intervention occurred, including any necessary infrastructure or relevant features
When and How Much	
8	Describe the number of times the intervention was delivered and over what period of time including the number of sessions, their schedule, and their duration, intensity, or dose
Tailoring	
9	If the intervention was planned to be personalised, titrated or adapted, then describe what, why, when, and how
Modifications	
10	If the intervention was modified during the course of the study, describe the changes (what, why, when, and how)
How well	
11	Planned: If intervention adherence or fidelity was assessed, describe how and by whom, and if any strategies were used to maintain or improve fidelity, describe them
12	Actual: If intervention adherence or fidelity was assessed, describe the extent to which the intervention was delivered as planned

Appendix 3

- Letter confirming sample size



Appendix 4

- Recruitment of therapists

RECRUITMENT

Randomised controlled trial to compare two methods of constraint induced movement therapy to improve functional ability in the affected upper limb in pre-school children with hemiplegic cerebral palsy.

I am currently recruiting therapy departments to be involved in this study.

Suitable participants are children with hemiplegic cerebral palsy who are aged between 18 months and 48 months

Would you like to be involved in this trial?

I would be happy to come and discuss the trial with you

If you would like further information please contact me on

[redacted]

- Placed on the 'Sharing Practice' module of the paediatric network of the Chartered Society of Physiotherapy interactive website (icsp; 01/10/2010)
- Paediatric therapy departments in West Midlands NHS trusts were sent a flyer
- Included in the conference pack of the National Conference of the Association of Paediatric Physiotherapy (2010)
- Sent to the College of Occupational Therapists Specialist Section for Children, Young People and Families to cascade to therapists

Appendix 5

Intervention paperwork

- Home information pack (CIMT using a cast and bandage)
- Application and management of the prolonged restraint
    - How to make the cast
    - Setting for application
    - Duration of application
    - Post removal assessment of the immobilised upper limb.
- Home information pack (CIMT using manual restraint). Home therapy instructions and diary the same as in the prolonged restraint group.

Constraint induced movement therapy(CIMT) using cast/splint and bandage

Home information pack

Name of therapist……

Contact number of therapist……

Days and times the therapist is

available……

Home Therapy Programme

- This therapy involves getting your childto actively use their affectedhand for about 60 minutes every day but not all at the same time.
- The unaffected handis not able to join in with playing in the sameway because of the splint/cast and bandage
- The affected handis encouraged to actively move by playing with a toy or doing an activity like finger feeding or helping to dress we do not want you to move their hand for them.
- Your therapists will help you by giving you ideas about what are suitable toys. We want this to be as enjoyable as possible.
- Successful play = easy toys that your child can use 

Make it fun and enjoyable so your child wants to repeat the activity

or keep on playing

Give them lots of encouragement

Instructions for parents/guardians during prolonged restraint using a cast and bandage

Your child has a cast and a bandage on their unaffected hand.

- It is important that the cast/bandage does not get wet. It does not matter if it just gets wet on the outside by e.g. rain. However if it gets soaking wet e.g. goes in the bath water it will get uncomfortable and will need to be changed. If this happens then could you please contact the therapist immediately. If the therapist is not available, then you will need to remove the cast and bandage yourself, in the way that the therapist has shown you. You will then need to contact your therapist as soon as they are available, to tell them what you have done, so that it can be replaced.

- The cast is made out of a material which is hard. It may be that the cast could cause some rubbing on the skin which can be sore and could possibly cause a blister. If your child is complaining that the cast is hurting or if they are saying that it is always hurting in the same place, the cast could be rubbing. If this happens then please contact your therapist immediately. The cast can be checked and possibly removed and replaced. If the therapist is not available then you will need to remove the cast yourself, in the way that the therapist has shown you. You will then need to contact your therapist as soon as

they are available, to tell them what you have done, so that it can be replaced.

- While your child is wearing the cast and bandage they may need extra supervision. This is because the hand that has the cast and bandage on, is the hand that they will probably hold out to protect themselves when they fall. This will not be so effective with the cast and bandage on. Therefore we would suggest that they may need more supervision when they are carrying out activities where they may fall. Or, these activities should be limited while they have the plaster and bandage on. Also extra care and supervision will be needed when they are playing with other children, as the cast is hard and if it comes into contact with another child may hurt them.

- We would like your child to wear the cast and bandage for the time that has been arranged however there may be an unexpected reason that it needs to come of. If this happens then that is fine your therapist can take it of and put it back on, more times than has been arranged.

- We would expect it to take some time for your child to get used to wearing the cast and bandage and at times they may get a bit agitated about it. However, if your child will not accept wearing the cast and bandage and is complaining, a lot of the time about wearing it, then

you need to contact your therapist immediately. We feel that if they continue complaining for about three or four days, then it may be better to discontinue with the cast and bandage and continue just with the therapy. We would like you to discuss this with your therapist and not stop it on your own.

- If there is another reason that you are unhappy about your child wearing the cast and bandage, then we would like you to contact your therapist immediately. However if your therapist is not available, then you can take the cast and bandage of yourself, you have been shown how to do this. If this happens can you please contact your therapist as soon as they are available, to let them know what you have done.

- If you require any advice about the cast and bandage, while it is on, then please contact your therapist. It is a good idea to look at the top of this sheet about when your therapist is available.

Daily Diary

- You will have already discussed with your therapist the dates when this therapy will begin and end.
- Just to remind you we aim that this therapy will take 6 weeks (42 days) but not all at the same time.
- We suggest that it will take place in three separate sessions of about 14 days each, with rest periods in between but the time can vary to suit you. However we do not want any session to be more than 21 days.
- The therapy has to be finished by 10 weeks after it started.

FILLING IN THE DIARY

- This diary is about how cooperative your child has been with the restraint using a cast/splint and bandage and with the therapy, and how long you managed to do the therapy for.

- The diary begins when the cast/splint and bandage are put on and the home therapy programme begins.
- We would like you to fill in the diary for each day ONLY when the restraint using a cast/splint and bandage and the home therapy programme has taken place.
- There are 2 questions for each day and one general question.
- Your therapist will need to collect the information from this diary sheet at a time that suits you both, they will discuss how and when it is collected with you.
- Please ask if there are any other questions.

Thank you

Active session

Did your child cooperate with the restraint using a cast/splint and bandage today?

Please circle

Day 1	Day2	Day3	Day4	Day5	Day6	Day7
Date	Date	Date	Date	Date	Date	Date
Always	Always	Always	Always	Always	Always	Always
Usually	Usually	Usually	Usually	Usually	Usually	Usually
About Half the Time	About Half the Time	About Half the Time	About Half the Time	About Half the Time	About Half the Time	About Half the Time
Seldom	Seldom	Seldom	Seldom	Seldom	Seldom	Seldom
Never	Never	Never	Never	Never	Never	Never

The therapy involves getting your child to actively use their affected hand for about 60 minutes but not all at the same time. How many minutes out of 60 did they manage to do today? Please circle

Day 1	Day2	Day3	Day4	Day5	Day6	Day7
Date	Date	Date	Date	Date	Date	Date
All 60 minutes	All 60 minutes	All 60 minutes	All 60 minutes	All 60 minutes	All 60 minutes	All 60 minutes
Nearly 60 minutes	Nearly 60 minutes	Nearly 60 minutes	Nearly 60 minutes	Nearly 60 minutes	Nearly 60 minutes	Nearly 60 minutes
About 30 minutes	About 30 minutes	About 30 minutes	About 30 minutes	About 30 minutes	About 30 minutes	About 30 minutes
Less than 30 minutes	Less than 30 minutes	Less than 30 minutes	Less than 30 minutes	Less than 30 minutes	Less than 30 minutes	Less than 30 minutes
Hardly at all	Hardly at all	Hardly at all	Hardly at all	Hardly at all	Hardly at all	Hardly at all

Have there been any problems this week because of the cast or the therapy? If yes, please describe

……

……

……

……

7

Did your child cooperate with the restraint using a cast/splint and bandage today? Please circle

Day 8	Day9	Day10	Day11	Day12	Day13	Day14
Date	Date	Date	Date	Date	Date	Date
Always	Always	Always	Always	Always	Always	Always
Usually	Usually	Usually	Usually	Usually	Usually	Usually
About Half the Time	About Half the Time	About Half the Time	About Half the Time	About Half the Time	About Half the Time	About Half the Time
Seldom	Seldom	Seldom	Seldom	Seldom	Seldom	Seldom
Never	Never	Never	Never	Never	Never	Never

The therapy involves getting your child to actively use their affected hand for about 60 minutes but not all at the same time. How many minutes out of 60 did they manage to do today? Please circle

Day 8	Day9	Day10	Day11	Day12	Day13	Day14
Date	Date	Date	Date	Date	Date	Date
All 60 minutes	All 60 minutes	All 60 minutes	All 60 minutes	All 60 minutes	All 60 minutes	All 60 minutes
Nearly 60 minutes	Nearly 60 minutes	Nearly 60 minutes	Nearly 60 minutes	Nearly 60 minutes	Nearly 60 minutes	Nearly 60 minutes
About 30 minutes	About 30 minutes	About 30 minutes	About 30 minutes	About 30 minutes	About 30 minutes	About 30 minutes
Less than 30 minutes	Less than 30 minutes	Less than 30 minutes	Less than 30 minutes	Less than 30 minutes	Less than 30 minutes	Less than 30 minutes
Hardly at all	Hardly at all	Hardly at all	Hardly at all	Hardly at all	Hardly at all	Hardly at all

Have there been any problems this week because of the cast or the therapy? If yes, please describe

……

……

Remember the rest period should be about now. Active sessions are about 14 days long with 14 days rest before the next active session.

Did your child cooperate with the restraint using a cast/splint and bandage today? Please circle

Day 15	Day16	Day17	Day18	Day19	Day20	Day21
Date	Date	Date	Date	Date	Date	Date
Always	Always	Always	Always	Always	Always	Always
Usually	Usually	Usually	Usually	Usually	Usually	Usually
About Half the Time	About Half the Time	About Half the Time	About Half the Time	About Half the Time	About Half the Time	About Half the Time
Seldom	Seldom	Seldom	Seldom	Seldom	Seldom	Seldom
Never	Never	Never	Never	Never	Never	Never

The therapy involves getting your child to actively use their affected hand for about 60 minutes but not all at the same time. How many minutes out of 60 did they manage to do today? Please circle

Day 15	Day16	Day17	Day18	Day19	Day20	Day21
Date	Date	Date	Date	Date	Date	Date
All 60 minutes	All 60 minutes	All 60 minutes	All 60 minutes	All 60 minutes	All 60 minutes	All 60 minutes
Nearly 60 minutes	Nearly 60 minutes	Nearly 60 minutes	Nearly 60 minutes	Nearly 60 minutes	Nearly 60 minutes	Nearly 60 minutes
About 30 minutes	About 30 minutes	About 30 minutes	About 30 minutes	About 30 minutes	About 30 minutes	About 30 minutes
Less than 30 minutes	Less than 30 minutes	Less than 30 minutes	Less than 30 minutes	Less than 30 minutes	Less than 30 minutes	Less than 30 minutes
Hardly at all	Hardly at all	Hardly at all	Hardly at all	Hardly at all	Hardly at all	Hardly at all

Have there been any problems this week because of the cast or the therapy? If yes, please describe

……
……
……
……

Did your child cooperate with the restraint using a cast/splint and bandage today? Please circle

Day 22	Day23	Day24	Day25	Day26	Day27	Day28
Date	Date	Date	Date	Date	Date	Date
Always	Always	Always	Always	Always	Always	Always
Usually	Usually	Usually	Usually	Usually	Usually	Usually
About Half the Time	About Half the Time	About Half the Time	About Half the Time	About Half the Time	About Half the Time	About Half the Time
Seldom	Seldom	Seldom	Seldom	Seldom	Seldom	Seldom
Never	Never	Never	Never	Never	Never	Never

The therapy involves getting your child to actively use their affected hand for about 60 minutes but not all at the same time. How many minutes out of 60 did they manage to do today? Please circle

Day 22	Day23	Day24	Day25	Day26	Day27	Day28
Date	Date	Date	Date	Date	Date	Date
All 60 minutes	All 60 minutes	All 60 minutes	All 60 minutes	All 60 minutes	All 60 minutes	All 60 minutes
Nearly 60 minutes	Nearly 60 minutes	Nearly 60 minutes	Nearly 60 minutes	Nearly 60 minutes	Nearly 60 minutes	Nearly 60 minutes
About 30 minutes	About 30 minutes	About 30 minutes	About 30 minutes	About 30 minutes	About 30 minutes	About 30 minutes
Less than 30 minutes	Less than 30 minutes	Less than 30 minutes	Less than 30 minutes	Less than 30 minutes	Less than 30 minutes	Less than 30 minutes
Hardly at all	Hardly at all	Hardly at all	Hardly at all	Hardly at all	Hardly at all	Hardly at all

Have there been any problems this week because of the cast or the therapy? If yes, please describe……
……
……

Remember the rest period should be about now. Active sessions are about 14 days long with 14 days rest before the next active session.

Did your child cooperate with the restraint using a cast/splint and bandage today? Please circle

Day 29	Day30	Day31	Day32	Day33	Day34	Day35
Date	Date	Date	Date	Date	Date	Date
Always	Always	Always	Always	Always	Always	Always
Usually	Usually	Usually	Usually	Usually	Usually	Usually
About Half the Time	About Half the Time	About Half the Time	About Half the Time	About Half the Time	About Half the Time	About Half the Time
Seldom	Seldom	Seldom	Seldom	Seldom	Seldom	Seldom
Never	Never	Never	Never	Never	Never	Never

The therapy involves getting your child to actively use their affected hand for about 60 minutes but not all at the same time. How many minutes out of 60 did they manage to do today? Please circle

Day 29	Day30	Day31	Day32	Day33	Day34	Day35
Date	Date	Date	Date	Date	Date	Date
All 60 minutes	All 60 minutes	All 60 minutes	All 60 minutes	All 60 minutes	All 60 minutes	All 60 minutes
Nearly 60 minutes	Nearly 60 minutes	Nearly 60 minutes	Nearly 60 minutes	Nearly 60 minutes	Nearly 60 minutes	Nearly 60 minutes
About 30 minutes	About 30 minutes	About 30 minutes	About 30 minutes	About 30 minutes	About 30 minutes	About 30 minutes
Less than 30 minutes	Less than 30 minutes	Less than 30 minutes	Less than 30 minutes	Less than 30 minutes	Less than 30 minutes	Less than 30 minutes
Hardly at all	Hardly at all	Hardly at all	Hardly at all	Hardly at all	Hardly at all	Hardly at all

Have there been any problems this week because of the cast or the therapy? If yes, please describe

……
……
……
……

Did your child cooperate with the restraint using a cast/splint and bandage today? Please circle

Day 36	Day37	Day38	Day39	Day40	Day41	Day42
Date	Date	Date	Date	Date	Date	Date
Always	Always	Always	Always	Always	Always	Always
Usually	Usually	Usually	Usually	Usually	Usually	Usually
About Half the Time	About Half the Time	About Half the Time	About Half the Time	About Half the Time	About Half the Time	About Half the Time
Seldom	Seldom	Seldom	Seldom	Seldom	Seldom	Seldom
Never	Never	Never	Never	Never	Never	Never

The therapy involves getting your child to actively use their affected hand for about 60 minutes but not all at the same time. How many minutes out of 60 did they manage to do today? Please circle

Day 36	Day37	Day38	Day39	Day40	Day41	Day42
Date	Date	Date	Date	Date	Date	Date
All 60 minutes	All 60 minutes	All 60 minutes	All 60 minutes	All 60 minutes	All 60 minutes	All 60 minutes
Nearly 60 minutes	Nearly 60 minutes	Nearly 60 minutes	Nearly 60 minutes	Nearly 60 minutes	Nearly 60 minutes	Nearly 60 minutes
About 30 minutes	About 30 minutes	About 30 minutes	About 30 minutes	About 30 minutes	About 30 minutes	About 30 minutes
Less than 30 minutes	Less than 30 minutes	Less than 30 minutes	Less than 30 minutes	Less than 30 minutes	Less than 30 minutes	Less than 30 minutes
Hardly at all	Hardly at all	Hardly at all	Hardly at all	Hardly at all	Hardly at all	Hardly at all

Have there been any problems this week because of the cast or the therapy? If yes, please describe

……

……

……

Thank you for taking part in this study. It has now finished and your child will continue with their usual therapy

Prolonged restraint with a short arm cast made with soft cast and using a crepe bandage

Preparation for application of prolonged restraint

Please discuss the instructions which are included, with the parents/guardians at the beginning of the session and, at the end of the session give these instructions to the parents/guardians to take home.

The Short Arm Cast Made With Soft cast

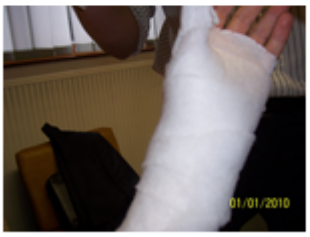
Materials:

- One roll of 3M softcast 2.5cm
- 3M Synthetic Stockinette 2.5cm
- 3M Synthetic Cast Padding 5cm
- Crepe bandage
- Tape to secure crepe bandage
- **Application of the cast:**
- Check the skin of the area that will be enclosed in the cast, for any open cuts. If there is an open cut then casting should be delayed until it is healed.
- Cut a piece of stockinette 5 cm longer than the distance required between below the metacarpal heads to above the wrist. Make a very small "nick" in this for the thumb to go through (see Picture 1).

Picture 1.

1

- Cut a piece of stockinette the length of the thumb. Cut up the side of the stockinette at the top and at the bottom. Place this on the thumb. (See Picture 2).
- Apply a layer of synthetic cast padding, using circular windings and using a 50% layering technique to the area to be casted (Picture 2).



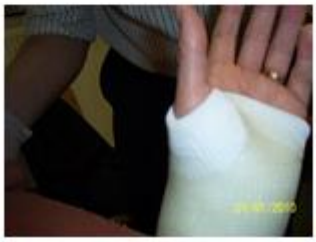
Picture 2

- The wrist joint should be positioned in neutral which is the position in which the hand "rests"
- Apply the first layer of soft cast from below the metacarpal heads to above the wrist, using circular windings and a 50% layering technique.
- Leave the fingers and the thenar eminence free of the cast.

When applying the soft cast around the thenar eminence, a diagonal cut needs to be made in the soft cast from one end, almost to the other end. This part of the soft cast is then placed around the thenar eminence, to help prevent any bulkiness and possible pressure areas (Picture 3).


Picture 3

- Fold the stockinette and padding back around the top, bottom and around the thenar eminence of the cast (Picture 4).


Picture 4

- Apply the second layer of soft cast using circular windings and a 50% layering technique (Picture 4).
- Wrap a wet bandage around the cast and leave it in place for about 2 minutes while the cast sets and then remove the bandage.
- When you are sure that the cast has completely set, the crepe bandage can be applied. To begin wrap the bandage loosely around the fingers to support them.

- Continue to wrap a crepe bandage around the fingers and thumb to completely enclose them, and secure with tape (Picture 5).

Picture 5

- If parents/guardians want to put a sock over the restraint to keep it clean that is perfectly acceptable.

Precautions with the application

During the application of soft cast, gloves must be worn and care should be taken to avoid contact with your unprotected skin, and that of the patient. This is because the resin will adhere to skin and clothing. It is recommended that you stand/sit facing the back of the arm /hand and apply the padding and soft cast from the inside outwards.

Setting

The prolonged restraint using a cast and bandage should be applied where possible in a clinic. It may be that in some circumstances this is not possible, in which case, it would be acceptable to do this at home.

Length of time in the prolonged restraint.

You will have agreed the dates for the prolonged restraint at the beginning of the trial, and where possible it would be helpful for this to continue as planned. However, you may find that the prolonged restraint, for a variety of reasons needs to be stopped and started more regularly than expected which is acceptable.
The child may take some time to accept the prolonged restraint, and show some frustration with it. However, in some circumstances there may be total non-acceptance of the prolonged restraint and it may be that you will need to discontinue it. If there is total non- acceptance by the child, the parents/guardians will make contact with you. You will need to monitor the child more closely, preferably on a daily basis, where possible. If this non-acceptance persists for about three to four days, following discussion with parents/guardians, it may be that you decide to discontinue with the prolonged restraint. If this is the case could you continue with the therapy and ensure that the child remains on the intervention arm of the trial.

Removal of the cast

Unwind the crepe bandage and remove. Then remove the cast by finding the end of the soft cast and unwind. The stockinette can be then be pulled off. The cast should be removed by unwinding, not cutting off. Give an explanation and demonstration on removing the prolonged restraint at the first session to the parents/guardians. When that has been done please tick and date below.

Assessment of the immobilised upper limb

At the end of every episode of immobilisation you need to carry out an inspection of the immobilised upper limb. This will include an assessment of the skin colour, the presence of any blistering or skin pressure areas and an assessment of joint ranges of movement (ROM). If there are any abnormal findings you will need to re-assess the upper limb and there needs to be an interval of at least 2 days before re-assessment. If there continues to be abnormal findings then the immobilisation will be discontinued.

Constraint induced movement therapy(CIMT) using manual restraint

Home Information pack

Name of therapist……

Contact number of therapist……

Days and times when the therapist is

available……

Manual Restraint
Instruction sheet

- Your child's unaffected hand is held gently during an activity to encourage them to use their affected hand.
- You may place your hand on top of your child's hand if they are playing at a table.
- Between any activities the hand is not held
- If they are playing on the floor you may chose to hold your child's hand or place your hand over your child's on the floor.
- This should be done on a little and often basis and you should aim to get your child playing at the same time.
- At no time is any force applied. If your child objects and starts to get upset then you should stop.
- This should only be carried out by you and your therapist will teach you how to do it.
- It may be that your therapist identifies another person that would be appropriate to do it as well. This could be a nursery /pre-school worker. With your agreement the therapists will train them on how to do this and they may carry this out when your child attends nursery.

Appendix 6

Outcome measures

Assisting Hand Assessment (AHA)

- Certification
- List of toys in kit
- Score sheet

Quality of Upper Extremity Skills Test (QUEST)

- Score sheet

Paediatric Quality of life Inventory (PedsQL) 4.0 Generic Core Scales

Score sheet

Paediatric Quality of life Inventory (PedsQL) 3.0 Cerebral Palsy Module

Score sheet

Paediatric Quality of Life Inventory (PedsQL) Infant Scales

Score sheet

Assisting Hand Assessment

AHA

CERTIFICATE

This is to verify that

Pauline Christmas

has completed the requirements of rater training and calibration for the Assisting Hand Assessment.

Rater No.: 679

Stockholm 2009-12-29

Lena Krumlinde Sundholm

Lena Krumlinde Sundholm, PhD OT
Course leader

AHA

Certificate

Hereby we declare that:

Name: P.M . Christmas

Born: January 2, 1958 in: England

Successfully fulfilled the certification procedure for the Assisting Hand Assessment after the AHA course from April 16-18, 2009, thus being a certified AHA rater.

Plaats : Amsterdam
Datum : april - august 2009
Study hours : 15

Cursist,

docent,
Lena Krumlinde Sundholm

docent,
Karin H Boeschoten

List of toys in the AHA suitcase

	Small-Kids AHA
Music box (adapted with a rubber band to elicit bimanual performance)	✓
Music machine with crank in plastic box (open the box and turn it upside down, put the music machine on top of the box and wind)	-
Prince/princess crown	✓
Maid's hat	✓
"Alien antennas"	-
Necklace	✓
Medal	✓
Bracelets	✓
Pull-the-string toy	✓
Saucepan with a lid (make sure the lid is on firmly to elicit bimanual performance)	✓
Small car/small object in tube	✓
Fabric pouch for marbles or toys (open the pouch, take out and put back the marbles, close the bag)	✓
Building toy made of Noppor/Clippo or Duplo (take apart, put together if relevant for the child's ability)	✓
Bottle with round bottom and marbles inside (put the marbles in the bottle)	✓
Cone with "peek-a-boo" toy	✓
Wooden cymbals	✓
Metal cymbals	✓
Thick markers and paper (take off the top and replace it — draw a little with at least two colors)	✓
Draw with markers from the pen case (draw with at least two colours)	-
Scissors (take out of the pen case and cut out the log or the ladder)	-
Fold a paper and/or **tear** it into long strips of paper	-

	Name				Hemi		Plex		right		left		-aff
	Date of examin.				Other diag.				right		left		-dom
	Date of birth				Play conductor:								
	Age	0yr	Months		Assessor:								
					Date of assess								

AHA

Assisting Hand Assessment, English version 4.4

				notes
GENERAL USAGE ITEMS	Approaches objects	4		
		3		
		2		
		1		
	Initiates use	4		
		3		
		2		
		1		
	Chooses AH when closer to objects	4		
		3		
		2		
		1		
ARM USE ITEMS	Stabilizes by weight or support	4		
		3		
		2		
		1		
	Reaches	4		
		3		
		2		
		1		
	Moves upper arm	4		
		3		
		2		
		1		
	Moves forearm	4		
		3		
		2		
		1		
GRASP - RELEASE ITEMS	Grasps	4		
		3		
		2		
		1		
	Holds	4		
		3		
		2		
		1		
	Stabilizes by grip	4		
		3		
		2		
		1		
	Readjusts grip	4		
		3		
		2		
		1		

GRASP - RELEASE	Varies type of grasp	4		
		3		
		2		
		1		
	Releases	4		
		3		
		2		
		1		
	Puts down	4		
		3		
		2		
		1		
FINE MOTOR ADJUSTMENT	Moves fingers	4		
		3		
		2		
		1		
	Calibrates	4		
		3		
		2		
		1		
	Manipulates	4		
		3		
		2		
		1		
COORDINATION	Coordinates	4		
		3		
		2		
		1		
	Orients objects	4		
		3		
		2		
		1		
PACE ITEMS	Proceeds	4		
		3		
		2		
		1		
	Changes strategies	4		
		3		
		2		
		1		
	Flow in task performance	4		
		3		
		2		
		1		
		Sum:		
		Scaled score %:	-33	
	Comments:			

ID#_____

Date:_____

PedsQL™

Paediatric Quality of Life Inventory

Version 4.0 – UK English

PARENT REPORT for **TODDLERS** (ages **2-4**)

DIRECTIONS

On the following page is a list of things that might be a problem for **your child**. Please tell us **how much of a problem** each one has been for **your child** during the **PAST MONTH** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

*In the **PAST MONTH**, how much of a **problem** has your child had with ...¶*

¶

PHYSICAL FUNCTIONING *(problems with...)*	Never	Almost Never	Some times	Often	Almost Always
1. Walking	0	1	2	3	4
2. Running	0	1	2	3	4
3. Participating in active play and exercise	0	1	2	3	4
4. Lifting heavy things	0	1	2	3	4
5. Bathing	0	1	2	3	4
6. Helping to pick up his or her toys	0	1	2	3	4
7. Having aches or pains	0	1	2	3	4
8. Feeling tired	0	1	2	3	4

¶

EMOTIONAL FUNCTIONING *(problems with...)*	Never	Almost Never	Some times	Often	Almost Always
1. Feeling afraid or scared	0	1	2	3	4
2. Feeling sad	0	1	2	3	4
3. Feeling angry	0	1	2	3	4
4. Having trouble sleeping	0	1	2	3	4
5. Worrying	0	1	2	3	4

¶

SOCIAL FUNCTIONING *(problems with...)*	Never	Almost Never	Some times	Often	Almost Always
1. Playing with other children	0	1	2	3	4
2. Other children not wanting to play with him or her	0	1	2	3	4
3. Getting teased by other children	0	1	2	3	4
4. Not able to do things that other children his or her age can do	0	1	2	3	4
5. Keeping up when playing with other children	0	1	2	3	4

¶

**Please complete this section if your child attends nursery or day care*¶

NURSERY/DAY CARE FUNCTIONING *(problems with...)*	Never	Almost Never	Some times	Often	Almost Always
1. Doing the same nursery/day care activities as peers	0	1	2	3	4
2. Missing nursery/day care because of not feeling well	0	1	2	3	4
3. Missing nursery/day care to go to the doctor or hospital	0	1	2	3	4

ID# _____

Date:_____

PedsQL™

Cerebral Palsy Module

Version 3.0

PARENT of TODDLER (ages **2-4**)

DIRECTIONS

Children with Cerebral Palsy sometimes have special problems. Please tell us **how much of a problem** each one has been for your child during the **past ONE month** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

*In the past **ONE month**, how much of a **problem** has this been for your child …*

DAILY ACTIVITIES *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Difficulty putting on his/her own shoes	0	1	2	3	4
2. Difficulty pulling a shirt on over his/her head	0	1	2	3	4
3. Difficulty brushing his/her own hair	0	1	2	3	4
4. Difficulty getting into the bathroom to use the toilet	0	1	2	3	4
5. Difficulty undressing to use the toilet	0	1	2	3	4

MOVEMENT AND BALANCE *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Difficulty moving one or both of his/her legs	0	1	2	3	4
2. Difficulty moving one or both of his/her arms	0	1	2	3	4
3. Difficulty moving parts of his/her body	0	1	2	3	4
4. Difficulty keeping his/her balance when sitting in a chair	0	1	2	3	4
5. Difficulty keeping his/her balance when standing	0	1	2	3	4

PAIN AND HURT *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Aches in joints and/or muscles	0	1	2	3	4
2. Having a lot of pain	0	1	2	3	4
3. Trouble sleeping because of pain or aching in joints and/or muscles	0	1	2	3	4
4. Muscles getting stiff and/or sore	0	1	2	3	4

FATIGUE *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Feeling tired	0	1	2	3	4
2. Feeling physically weak (not strong)	0	1	2	3	4
3. Needing to rest a lot	0	1	2	3	4
4. Feeling that he/she doesn't have enough energy to do things that he/she likes to do	0	1	2	3	4

EATING ACTIVITIES *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Difficulty eating with a spoon and/or fork	0	1	2	3	4
2. Difficulty chewing his/her food	0	1	2	3	4
3. Difficulty holding a cup	0	1	2	3	4
4. Difficulty drinking on his/her own	0	1	2	3	4

ID# _____

Date:_____

PedsQL™

Pediatric Quality of Life Inventory

Infant Scales

PARENT REPORT for INFANTS (ages 13-24 months)

DIRECTIONS

On the following page is a list of things that might be a problem for **your child**. Please tell us **how much of a problem** each one has been for **your child** during the **past ONE month** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

*In the past **ONE month,** how much of a **problem** has your child had with …*

PHYSICAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Low energy level	0	1	2	3	4
2. Difficulty participating in active play	0	1	2	3	4
3. Having hurts or aches	0	1	2	3	4
4. Feeling tired	0	1	2	3	4
5. Being lethargic	0	1	2	3	4
6. Resting a lot	0	1	2	3	4
7. Feeling too tired to play	0	1	2	3	4
8. Difficulty walking	0	1	2	3	4
9. Difficulty running a short distance without falling	0	1	2	3	4

PHYSICAL SYMPTOMS *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Having gas	0	1	2	3	4
2. Spitting up after eating	0	1	2	3	4
3. Difficulty breathing	0	1	2	3	4
4. Being sick to his/her stomach	0	1	2	3	4
5. Difficulty swallowing	0	1	2	3	4
6. Being constipated	0	1	2	3	4
7. Having a rash	0	1	2	3	4
8. Having diarrhea	0	1	2	3	4
9. Wheezing	0	1	2	3	4
10. Vomiting	0	1	2	3	4

EMOTIONAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Feeling afraid or scared	0	1	2	3	4
2. Feeling angry	0	1	2	3	4
3. Crying or fussing when left alone	0	1	2	3	4
4. Difficulty soothing himself/herself when upset	0	1	2	3	4
5. Difficulty falling asleep	0	1	2	3	4
6. Crying or fussing while being cuddled	0	1	2	3	4
7. Feeling sad	0	1	2	3	4
8. Difficulty being soothed when picked up or held	0	1	2	3	4
9. Difficulty sleeping mostly through the night	0	1	2	3	4
10. Crying a lot	0	1	2	3	4
11. Feeling cranky	0	1	2	3	4

.

*In the past **ONE month**, how much of a **problem** has your child had with …*

SOCIAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Not smiling at others	0	1	2	3	4
2. Not laughing when tickled	0	1	2	3	4
3. Not making eye contact with a caregiver	0	1	2	3	4
4. Not laughing when cuddled	0	1	2	3	4
5. Being uncomfortable around other children	0	1	2	3	4

COGNITIVE FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Not imitating caregivers' actions	0	1	2	3	4
2. Not imitating caregivers' facial expressions	0	1	2	3	4
3. Not imitating caregivers' sounds	0	1	2	3	4
4. Not able to fix his/her attention on objects	0	1	2	3	4
5. Not imitating caregivers' speech	0	1	2	3	4
6. Difficulty pointing to his/her body parts when asked	0	1	2	3	4
7. Difficulty naming familiar objects	0	1	2	3	4
8. Difficulty repeating words	0	1	2	3	4
9. Difficulty keeping his/her attention on things	0	1	2	3	4

Appendix 7

- Patient information sheet
- Patient Advisory Liaison Service information sheet

Patient Information Sheet

Your child has been invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear to you or if you would like more information. Take time to decide whether or not you would like to take part.

My name is Pauline Christmas. I am a Consultant physiotherapist and work for the Children and Families Division of South Birmingham Community Health. I am leading this research study which will be evaluated for my PhD. I am called the chief investigator. The study is funded by the West Midlands Strategic health Authority. If you would like to contact me please feel free to do so. My contact details are at the end of this document.

What is the purpose of the study?

Constraint induced movement therapy (CIMT) aims to improve the use of an affected hand and arm (upper limb) in people who tend to use one hand more than the other such as with hemiplegic cerebral palsy (HCP). It involves stopping the unaffected upper limb being used and encouraging lots of use of the affected upper limb. A number of studies have been carried out to investigate the use of constraint induced movement therapy in children with HCP.

We want to know if CIMT which uses prolonged restraint is better than CIMT which uses manual restraint. Prolonged restraint is when a wrist cast/splint and bandage is put on the child's unaffected upper limb to stop it being used and left on for a period of time. Manual restraint is when the child's unaffected upper limb is gently held by an adult to stop it being used intermittently over a set period of time.

Both of these methods would include lots of encouragement to use the affected upper limb through play and daily activities such as feeding.

Currently there is no good evidence as to which method is best. The study aims to answer the question: Does CIMT used as part of routine therapy within a National Health Service (NHS) setting improve the affected upper limb in the young child with HCP and does this improvement persist?

How old are the children in the study?

We are only including children who have not started their compulsory education yet. This is because we do not want the therapy to interfere with their education.

How long will my child be in the study?

The CIMT will last for 10 weeks. At the beginning of the 10 weeks and at the end of the 10 weeks your child's upper limb will be assessed. During the 10 weeks there will be active periods where your child would receive CIMT and passive periods where they do not receive CIMT. These periods would be expected to be 2 week blocks however that can be flexible to fit in with your family life. The total time that they would receive CIMT would be 6 weeks. CIMT would then stop and your child would continue to receive their usual therapy. 24 weeks after the CIMT began your child would then be re-assessed.

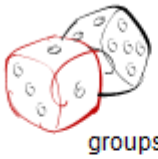
Why is my child suitable?

The study will include 60 children with HCP. Your child has a diagnosis of HCP and is not yet at school.

Does my child have to take part?

No, it is up to you whether or not your child takes part. If you decide they are not to take part their therapy will not be affected in any way. If you do decide they can take part, you will be given this information sheet to keep and be asked to sign a consent form. If you decide they can take part you are still free to withdraw them at any time and without giving a reason, although it would be very helpful, with your agreement that they may continue to give information. A decision to withdraw at any time or a decision not to take part will not affect the standard of care that your child receives.

What will happen to my child if they take part?



This is a randomised study. Sometimes, we do not know which way of treating patients is best therefore we need to make comparisons. Children in the study will be put into two groups. The groups are selected at random. Children in each group will have a different treatment and these are compared. If you decide they can take part your child will be allocated at random to receive either CIMT using a splint/cast and bandage for a prolonged period or using manual holding for a brief period. Your child will have a 50:50 chance of being in either group.

You will have the opportunity to talk about the research with a therapist where your child receives their therapy. This could be the therapist who treats your child or it could be the therapist who is leading the study in the local area. The therapist who is leading the study in your local area is called the principle investigator and her name and telephone number is ……

There are also organizations that you can talk to about the study such as the patient advice liaison service (PALS) (Free phone 0800 9172855).

If you decide they can take part the therapist where your child receives their therapy will invite you back to the clinic. You will be asked to sign a consent form. Two assessments will be carried out on your child's upper limb by the therapist who is leading the research. One of these assessments will include making a DVD of your child playing at a table and will take about 20 minutes. The other will assess both upper limbs and will take about 30 minutes to complete. You will also be asked to complete two questionnaires. One is in two parts and altogether will take about 30 minutes. The second one will take about 5 minutes. You will be given some written information about a home programme of therapy that you will need to do at home during the CIMT and information about a daily diary that you

will need to keep. You will decide with your therapist the dates that you want the CIMT to begin and the dates for the active and passive periods.
Your child will be allocated at random to receive either CIMT using a splint/cast and bandage or using manual holding. Then you will be invited back to clinic within one month of the last clinic appointment. Depending on which group your child was allocated to, your child will either have the wrist/cast and bandage applied to their unaffected upper limb, or you will be shown how to hold your child's unaffected upper limb to help stop them using it. The therapist will then go over the home programme of therapy that you will be expected to do using the information that you have already been given and how to complete the daily diary. On average it would be expected that during the active period your child would do about one hour, not necessarily all at the same time through the day of therapy with their affected hand. This would mainly be with you although you will receive guidance from a therapist. If your child attends nursery it may be that your therapist identifies somebody that she can teach to also carry out some of the therapy at the nursery.

It would be expected that you would keep a daily diary which would take about 5 minutes to complete each day. This would be to record the amount of restraint of the unaffected upper limb (both with the cast/splint and with manual restraint), the acceptance of the restraint and the amount of therapy that has been carried out that day with the affected upper limb.
Your therapist/therapy assistant would be in contact each week either face to face or on the telephone. They will offer any advice, answer any questions and collect the information from the daily diary. They will also ask specific questions about the therapy and the restraint which would take about 15 minutes to complete. You will have a telephone contact that you can use during normal working hours for advice. If your child has had a cast/splint and bandage applied you will be given written information about how to manage any problems with the cast/splint and you will be shown how to remove this in case there is a problem which you could do at any time.

After 10 weeks from when the CIMT began your child will be invited back to clinic and two separate assessments on their upper limb will be repeated. One of these assessments will include making a DVD of your child playing at a table and will take about 20 minutes. The other will assess both upper limbs and will take about 30 minutes to complete. These assessments will be carried out by the therapist leading the research. You will also be asked to complete the same two questionnaires as you did in the beginning of the study. The first one is in 2 parts and takes about 30 minutes and the second one will take about 5 minutes. The CIMT will then be finished and your child will continue with their usual therapy. Twenty four weeks after the study began you will receive a copy of the two questionnaires that you have already completed in the post. The first one takes about thirty minutes and the second one about 5 minutes. You will be asked to complete these and return them in a pre-paid envelope. Your therapists can help you with this.

If your child had manual restraint and you wanted them to try the cast/splint method of restraint you will be able to do that after the final assessment.

What are the possible disadvantages and risks of taking part?

We do not anticipate any disadvantages of taking part. It may be that your child gets frustrated at wearing a restraint to stop the use of the unaffected hand. However appropriate guidance from the therapist about the type of toys to use and adapting activities would help to reduce that frustration. Your involvement to carry out the therapy can be time consuming. However where possible if your child attends any other places such as a nursery we would hope to get these staff also carrying out these activities with guidance from the therapist. Many parents/guardians already do a great deal to encourage their child to use their affected hand. It may be that using the restraint, parents feel that this reduces the possible reminders and encouragement that they frequently need to give.

What if something goes wrong?

If you are harmed by taking part in this research then this would be reported as an NHS incident in the same way as any other incident which may occur in the NHS. However there are no special compensations arrangements. If you are harmed by somebody's negligence then you may have grounds for a legal action but you would have to pay for it. Regardless of this, if you wish to complain or have any concerns about any aspects of the way you have been approached or treated during the course of this study the normal NHS complaints mechanisms are available for you. If you have concerns about any aspect of this study you should ask to speak to the therapist who is responsible for the research in your area who will do their best to answer your questions. (Local PI name here). If you remain unhappy and wish to complain formally you can contact your local patient advice liaison service (PALS) (Local PALS telephone number).

Will my child taking part in this study be kept confidential?

All information collected about your child in the study will remain strictly confidential in the same way as their other medical records. Personal information will not be used on the research records or on the DVD instead a number which is unique to your child will be used.

We would like your permission to tell your GP and community consultant that your child is taking part in the study. Your child may still take part if you do not want us to contact your GP and community consultant.

Some of the DVDs that have been made of your child's hand assessment will be scored by a therapist who is trained in using that hand assessment who works for a different NHS trust. The DVDs will be made secure using a password and posted using a tracking service. We would like your permission to be able to do this.

All of the information that will be collected from the research including the DVDs will be stored for 5 years after the study finishes in a secured/locked cupboard. This is so that if there were any questions that needed to be answered after the

study finished the information from the study could be made available. After this time the information will be destroyed.

What will happen to the results of the research study?

The results of the study will be published in a medical journal after the study has been completed but your child will not be identified in any report or publication. Parents who have children with HCP are part of the study team and will help us share this information with the wider cerebral palsy community.

Who is organizing and funding the research?

The study is being funded as part of a clinical research fellowship which is being provided by the West Midlands Strategic Health Authority.

Who has looked at the research?

All research in the NHS is looked at by an independent group of people called a Research Ethics Committee whose role is to protect your safety, rights well being and dignity

If you decide to take part in the study you will be given a copy of this information sheet and a signed consent form to keep.

Contact information

Pauline Christmas Chief Investigator. P.christmas@nhs.net 07973 362792

Principle investigator (Local area)

Name……email……

Tel:……

Patient Information Liaison Service. Free phone 0800 917 2855

NHS
South Birmingham Community Health

Patient Advice & Liaison Service (PALS)

When you need confidential advice, have concerns, or don't know where to turn, we are here to help

সাহায্যের জন্য এখানে BENGALI

我們旨在提供協助 CHINESE

અમે મદદ કરશું GUJARATI

हम यहां सहायता के लिए हैं। HINDI

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مدد کے لیئے تیار URDU

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How to contact us

Freephone 0800 917 2855
Minicom 0121 449 8352
Text 07540 702477
Email PALS@sbpct.nhs.uk
Write to PALS, Moseley Hall Hospital, Alcester Road, Moseley, Birmingham, B13 8JL

The service is available between 9.00am – 5.00pm Monday to Friday. Outside these hours messages can be left. We aim to offer a service that meets your needs.

For your health and comfort we are smoke free. Staff, patients and visitors are kindly asked not to smoke on our premises.

Appendix 8

Trial Steering and Data Monitoring Committee

Membership·of·the·Trial·Steering·and·Data·Monitoring·Committee¶
[1]·Birmingham·Community·Healthcare·Trust·····[2]·University·of·Birmingham¶

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Membership¤	Employment¶ ¤	Role· in· the· CATCH· trial¤	¤
Dr·Anne·Aukett·(AA)¶ (Independent·chair)¤	Community·Paediatrician¶ (Retired)·[1]¤	¤	¤
Pauline·Christmas·(PC)¶ ¤	Paediatric·physiotherapist[1]¤	Investigator¤	¤
Professor·Cath·Sackley·¤	Professor· of· physiotherapy· research·[2]¤	Investigator¤	¤
Dr·Carole·Cummins·(CC)¤	Senior·lecturer[2]¶ ¤	Investigator¤	¤
Dr·Tom· Hoppitt·(TH)¤	Research·fellow[2]¶ ¤	Trial·Coordinator¤	¤
Dr·Max·Feltham·(MF)¤	Research·fellow[2]¶ ¤	Trial·Coordinator¤	¤
Christel·Cooper¤	Paediatric·physiotherapist[1]¤	Intervention·therapist¶ ¤	¤
Jacqui·Parker¶ ¤	Paediatric·physiotherapist[1]¤	Intervention·therapist¤	¤
Julie·Markell¤	¤	Patients,· public· involvement· representative¶ ·¤	¤
Carole·Maddox¤	Patient· advisory· liaison· service·(PALS)·employee[1]¤	PALS·representative·¤	¤
Zarina·Mansuri·¤	Patient· advisory· liaison· service·(PALS)employee[1]¤	PALS·representative¤	¤

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Appendix 9

Systematic review

- Checklist for reporting a systematic review
- Excluded controlled trials
- Data extraction tool
- Data extracted from included studies

Table 1. **Checklist of Items to Include When Reporting a Systematic Review (With or Without Meta-Analysis)**

Section/Topic	Item #	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see Item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

Excluded controlled trials which investigated CIMT in the CP population with reasons for exclusion (n=35)

		n	Mean age (y. m)	Reason for exclusion				
				Age	Diagnosis	Intervention	Comparator	Outcome
1	Abd El-Kafy, E. M. et al., (2014) Effect of constraint-induced therapy on upper limb functions: a randomized control trial. **Scandinavian journal of occupational therapy**, 21 (1):11-23.	30	4.0-8.0 (range)	x			6 hours daily intensive therapy	
2	Charles, J. R. et al., (2006) Efficacy of a child-friendly form of constraint-induced movement therapy in hemiplegic cerebral palsy: A randomized control trial. **Developmental Medicine and Child Neurology**, 48 (8):635-642.	22	6.8 (SD 1.4)	X				
3	Chen, C. L., et al., (2013) Effect of therapist-based constraint-induced therapy at home on motor control, motor performance and daily functions in children with cerebral palsy: a randomized controlled study. **Clinical rehabilitation**, 27 (3):236-245.	47	8.7	X				
4	Eugster-Buesch, F., et al., (2012) Forced-use therapy for children with cerebral palsy in the community setting: A single-blinded randomized controlled pilot trial. **Journal of Pediatric Rehabilitation Medicine**, 5 (2):65-74.	23	9.8 (CIMT) 11.7 (control)	X				
5	Hosseini, S. A., et al., (2012) Effects of a combination of constraint induced movement therapy with bimanual approach on fine motor skills in 5-10 year old hemiplegic children. **European Journal of Neurology**, (19) Conference abstract p.567.	25	7.8 (CIMT) 7.1 (control)	X		Hybrid CIMT		
6	Hsin, Y. J., et al., (2012) Efficacy of constraint-induced therapy on functional performance and health-related quality of life for children with cerebral palsy: A randomized controlled trial. **Journal of Child Neurology**, 27 (8):992-999.	22	6.0-8.0 (range)	X				
7	Jaeho, Y.U., et al., (2012) Effects of Modified Constraint-induced Movement Therapy on Hand Dexterity, Grip Strength and Activities of Daily Living of Children with Cerebral Palsy: a Randomized Control Trial. **Journal of Physical Therapy Science**, (10) 1029-1031.	20	9.4 (SD 0.3)	X				
8	Motta, F., et al., (2010) Forced-use, without therapy, in children with hemiplegia: Preliminary study of a new approach for the upper limb. **Journal of Pediatric Orthopaedics**, 30 (6):582-587.	20	5.6-8.8 (range)	X		No therapy		
9	Sakzewski, Let al., (2009) One hand or two? Randomised trial of constraint induced movement therapy versus bimanual training for children with congenital hemiplegia **Developmental Medicine and Child Neurology**, (51) conference abstract p. 57.	46	10.7	X			BIM	
10	Sakzewski, L., et al., (2011) Randomised trial of constraint-induced movement therapy and bimanual training on activity outcomes for children with congenital hemiplegia. **Developmental Medicine & Child Neurology**, 53 (4):313-320.	63	10.2	X			BIM	

				Age	Diagnosis	Intervention	Comparator	Outcome
11	Aarts, P. B., et al., (2010) Effectiveness of modified constraint-induced movement therapy in children with unilateral spastic cerebral palsy: A randomized controlled trial. **Neurorehab and Neural Repair**, 24 (6):509-518.	52	5.0			Hybrid CIMT		
12	Boyd, R. N., et al., (2013) Randomised trial of the density and context of upper limb intensive group compared to individualised training for children with congenital hemiplegia **Developmental Medicine and Child Neurology**, (55) conference abstract p. 8.	48	7.9			Hybrid CIMT		
13	De Brito Brandao, M., et al., (2010) Adapted version of constraint-induced movement therapy promotes functioning in children with cerebral palsy: a randomized controlled trial. **Clinical rehabilitation**, 24 (7):639-647.	16	5.6 (CIMT) 6.7 (control)			Hybrid CIMT		
14	Koseotlu, P. K., et al.,(2013) Comparison of the effects of modified constraint induced movement therapy combined with bimanual training, with modified constraint movement therapy approaches in the upper extremity functions in children with unilateral cerebral palsy, Unilateral [Turkish, English]. **Turkiye Fiziksel Tip Rehabilitasyon Dergisi**, (59) conference abstract p. 232.	32	-			Hybrid CIMT		
15	Lowes, L. P., et al., (2014) Pilot study of the efficacy of constraint-induced movement therapy for infants and toddlers with cerebral palsy. **Phys Occup Ther Pediatr**, 34 (1):4-21.	5	0.7-1.6 (range)			Hybrid CIMT		

				Age	Diagnosis	Intervention	Comparator	Outcome
16	Eliasson, A. C., et al., (2009) Feasibility of a day-camp model of modified constraint-induced movement therapy with and without botulinum toxin A injection for children with hemiplegia. **Physical and Occupational Therapy in Pediatrics**, 29 (3):311-333.	16	8.0-17.0 (range)			CIMT with botulinum toxin injections	CIMT	
17	Gillick, B. T., et al., (2014) Primed low-frequency repetitive transcranial magnetic stimulation and constraint-induced movement therapy in pediatric hemiparesis: a randomized controlled trial. **Dev Med Child Neurol**, (56) 44-52	19	10.10			CIMT with repetitive transcranial magnetic stimulation	CIMT with sham repetitive transcranial magnetic stimulation	
18	Park, E. S., et al., (2009) The short-term effects of combined modified constraint-induced movement therapy and botulinum toxin injection for children with spastic hemiplegic cerebral palsy. **Neuropediatrics**, 40 (6):269-274.	32				CIMT with botulinum toxin injections	Botulinum toxin injections	
19	Xu, K., et al., (2012) Efficacy of constraint-induced movement therapy and electrical stimulation on hand function of children with hemiplegic cerebral palsy: a controlled clinical trial. **Disability and rehabilitation**, 34 (4):337-346	68	2.0-14.0 (range)			CIMT with electrical stimulation	CIMT	
20	Kirton, A., et al., (2012) Brain stimulation and constraint for perinatal stroke hemiparesis: Interim safety and feasibility in the PLASTIC CHAMPS trial. **Developmental Medicine and Child Neurology**, (54) conference abstract p.154.	45	11.4	X		CIMT with repetitive transcranial nerve stimulation		

				Age	Diagnosis	intervention	Comparator	Outcome
21	Brandao, M. D., et al.,(2011) The effects of constraint-induced movement therapy (CIMT) and hand-arm bimanual intensive training (HABIT) on the daily functioning of children with cerebral palsy. **Developmental Medicine and Child Neurology** (53) conference abstract p. 30.	16	5.6				HABIT	
22	Case-Smith, J., et al., (2012) Multicentre randomized controlled trial of pediatric constraint-induced movement therapy: 6-Month follow-up. **American Journal of Occupational Therapy**, 66 (1):15-23.	18	4.1			Hybrid CIMT 6 hours per day	Hybrid CIMT 3 hours per day	
23	Deppe, W., et al., (2013) Modified constraint-induced movement therapy versus intensive bimanual training for children with hemiplegia-A randomized controlled trial. **Clinical Rehabilitation**, 27 (10):909-92	47	3.3-11.4 (range)				BIM	
24	Gelkop, N., et al., (2013) Constraint-induced movement therapy and bimanual training in children with hemiplegic cerebral palsy provided in a special education preschool and kindergarten setting. **Developmental Medicine and Child Neurology**, (55) conference abstract p. 8.	12	1.5-7.0			Hybrid CIMT	BIM	
25	Gordon, A.M., et al., (2008) Both constraint-induced movement therapy and bimanual training lead to improved performance of upper extremity function in children with hemiplegia. **Developmental Medicine & Child Neurology**, 50 (12):957-958.	16	7.0				HABIT	

				Age	Diagnosis	Intervention	Comparator	Outcome
26	Gordon, A. M., et al., (2011) Bimanual training and constraint-induced movement therapy in children with hemiplegic cerebral palsy: a randomized trial. **Neurorehabil Neural Repair**, 25 (8):692-702.	42	6.0				HABIT	
27	Hoare, B., et al.,(2012) Bimanual occupational therapy is as effective as modified constraint-induced therapy following Botulinum toxin-A in young children with hemiplegic cerebral palsy. **Developmental Medicine and Child Neurology**, (54) 37-38.	34	3.0 (SD 1.4)			CIMT with botulinum toxin injections	BOT with botulinum toxin injections	
28	Hung, Y., et al., (2010) Both intensive bimanual and unimanual training improve unimanual reach-grasp-eat movement control in children with hemiplegia. **Developmental Medicine and Child Neurology**, (52) 26-27.	12	5.0-12.0 (range)	X			HABIT	
29	Klingels, K., et al., P. (2013) Randomized trial of modified constraint-induced movement therapy with and without an intensive therapy programme in children with unilateral cerebral palsy. **Developmental Medicine and Child Neurology**, (55) conference abstract p. 18.	51	8.9	X		Hybrid CIMT	Restraint only	
30	Lin, K. C., et al., (2011) Effects of home-based constraint-induced therapy versus dose-matched control intervention on functional outcomes and caregiver well-being in children with cerebral palsy. **Research in Developmental Disabilities**, 32 (5):1483-1491.	21	4.0-9.9 (range)			CIMT with unimanual training	CIMT with unimanual/ bimanual training	

				Age	Diagnosis	Intervention	Comparator	Outcome
31	Vaghela, V.G. (2014) To study the effects of Mcimt versus CIMT for young children with Spastic Hemiplegic Cerebral palsy-A comparative study. **Indian Journal of Physiotherapy and Occupational therapy**, 8 (2):136-41.	30					MCIMT (one hour per day)	
32	Wallen, M., et al., (2012) Modified constraint-induced therapy compared with intensive occupational therapy for children with hemiplegic cerebral palsy: Results of a randomised trial. **Developmental Medicine and Child Neurology**, (54) 36-37.	50	4.6				Intensive OT	
33	Rostami, H. R., Malamiri, R. A. (2012) Effect of treatment environment on modified constraint-induced movement therapy results in children with spastic hemiplegic cerebral palsy: a randomized controlled trial. **Disability and rehabilitation**, 34 (1):40-44.	14	6.2				CIMT clinic	
34	ΔDeluca, S. C., et al.,(2006) Intensive pediatric constraint-induced therapy for children with cerebral palsy: Randomized, controlled, crossover trial. **Journal of Child Neurology**, 21 (11):931-938.	18	3.6			Not HCP		
35	ΔSung, I.-Y., et al., (2005) Efficacy of Forced-Use Therapy in Hemiplegic Cerebral Palsy. **Archives of Physical Medicine and Rehabilitation**, 86 (11):2195-2198.	31	2.9 (CIMT) 3.7 (control)					X§

Hand-arm bimanual intensive therapy (HABIT); CIMT plus bimanual (Hybrid CIMT); Bimanual therapy (BIM); Occupational therapy (OT); Bimanual occupational therapy (BOT); Hemiplegic cerebral palsy (HCP); Δ Identified from the Cochrane systematic review (Hoare et al., 2007); § 1) Wee FIM evaluates participation restriction (Ottenbacher et al., 1997).2) Erhardt Developmental Prehension Assessment (developed for children <2 years) (Erhardt, 1994) 3) Box and block test. Psychometric properties not suitable for children with CP (Mathiowetz et al., 1985)

Data extraction tool (Higgins and Green 2011)

Study ID. Methods. Study design. Total study duration. Sequence generation. Allocation sequence concealment. Blinding. Other concerns about bias. Participants. Total number. Setting. Diagnostic criteria. Age. Sex. Country. [Co-morbidity]. [Socio-demographics]. [Ethnicity]. [Date of study]. Interventions. Total number of intervention groups. *For each intervention and comparison group of interest*: Specific intervention. Intervention details (sufficient for replication, if feasible).	Outcomes. Outcomes and time points *For each outcome of interest*: Outcome definition Unit of measurement (if relevant). For scales: upper and lower limits, and whether high or low score is good. Results. Number of participants allocated to each intervention group. *For each outcome of interest*: Sample size. Missing participants. Summary data for each intervention group. Means and SDs for continuous data. Difference in means (SD) from baseline to immediate post-intervention. Key conclusions of the study authors.

Data extracted from included studies using data extraction tool (Higgins and Green 2011)	
Study ID	**Choudhary et al., 2013**
Study design	Randomised controlled trial
Study duration (weeks)	12
Randomisation Group generation	Computer generated number sequence (block size of 6). No stratification. Not specified who conducted.
Allocation concealment	Not described. Assessor had direct contact with the participants and caregivers
Blinding	Assessor and therapist teaching the interventions to the caregivers blinded.
Other concerns about bias	
Participants	
Total number	31
Setting	
Diagnostic criteria	1) Hemiplegic cerebral palsy. 2) Aged 3-8 years 3) Minimum difference of 10 total test score on QUEST between both upper limbs. 4) Understands simple commands 5)Sits without support.6) Can see 1 inch^2 from 1 meter distance Excluded: 1) Uncontrolled epilepsy (>one episode per month during past 3 months) 2) Ashworth scale for spasticity ≥ 3 at shoulder, elbow or wrist 3) Orthopaedic surgery/casting/splinting of upper limb in preceding 6 months 4) Botulinum toxin or Phenol block in upper limb in preceding 6 months or anticipated during study 5) Receiving tone modifying agents such as Baclofen.
Age Mean (±SD). Months	CIMT 58.5 (±17.7) Control 62.7 (±18.0)
Sex	18 boys 13 girls
Country	India
Co-morbidity	Seizures (13) CIMT (6) Control (7). Microcephaly (3) CIMT (2) Control (1)
Socio-demographic	
Ethnicity	Indian
Date of study	Conducted from April 2008 – September 2009
Interventions	
Total number of intervention groups	2 groups
Each intervention group	CIMT
Specific intervention	2-hours of supervised intervention per day for 10 days, over a 4 week period, In a hospital Intervention by occupational therapist (OT) and the first investigator Delivered in small groups, with 4 participants per group. Unaffected upper limb restrained with an arm-sling Affected upper limb practiced specific movements with a time constraint. Once performed successfully the task was made more difficult Verbal praise given throughout At the end of the supervised session, the child practised at home with the caregivers using restraint of the unaffected upper limb and an exercise plan, for 1 hour. This was extended to 2 hours per day when it was a day of non-supervised intervention. Children also received the conventional therapy.
Each intervention group	Control
Specific intervention	Conventional therapy 20 minutes per day at home provided by caregiver. Included stretching and strengthening exercises (bilateral activities and

1

	activities of daily living). Taught by an OT.
Outcomes	
Outcomes and time points	Quality of upper extremity skills test (QUEST) at 4 weeks post intervention start date
Outcome definition	QUEST evaluates quality of upper extremity function in 4 domains: dissociated movement; grasp; protective extension and weight-bearing for children with neuromotor dysfunction aged 18 months to 8 years.
Unit of measurement	2(able to complete item) 1(Unable to complete item 1(not-tested) Scores summed
Upper and lower limits and whether high or low score is good	Upper limit =100.Lower=0 High score =good
Results	
Number of participants allocated to each group	CIMT(16) Control (15)
Outcome	QUEST at 4 weeks post intervention
Sample size	CIMT (15) Control (15)
Missing participants	1
Baseline scores. Mean (±SD)	QUEST (CIMT 76.4 (±9.8) Control 81.1 (± 9.5)
Change score from-baseline to immediately post intervention. Mean (±SD)	QUEST (CIMT 10.7(±5.2) Control 1.4 (±1.7)
Final value scores immediately post-intervention Mean (±SD)	QUEST (dissociated movement) CIMT 83.5(±10.8) Control 81.6(±12.2) QUEST (grasp) CIMT 83.1(±10) Control 76.3 (±9.3) QUEST (weight-bearing) CIMT 92.0(±10.4) Control 88.1 (±12.7) QUEST (protective extension) CIMT 90.1(±10.1) Control 84.0 (±10.6)
Estimate of effect(95%CI)	d =2.4 (C-3.4.-1.5)
Key conclusions	A significant difference between intervention and control groups on the QUEST
Study ID	**Al-Oraibi&Eliasson, 2011**
Study design	Randomised controlled trial
Study duration(weeks)	8
Randomisation (Group)	Procedure not described but conducted by first author and study coordinator. Stratification by age and motor ability (classified by the Manual ability classification system (MAC) level).
Allocation concealment	Video assessments analysed by a therapist unaware of the study aims and group allocation)
Blinding	Video assessments scored by a therapist blind to study aims and to group allocation.
Other concerns about bias	30% (6/20) dropped out not specified from which group. 2 due to technical problems; 4 difficult to access clinic.
Participants	
Total number	20
Setting	Clinic and home setting
Diagnostic criteria	1)Hemiplegic cerebral palsy 2) Normal intellectual ability 3)Family likely to cooperate
Age Mean (±SD). Months	
Sex	10 boys 4 girls
Country	Jordon
Co-morbidity	Seizures (1) CIMT (0) NDT (1) Speech impairment (2) CIMT(0) NDT (2)
Socio-demographic	
Ethnicity	Jordanian
Date of study	

Interventions	
Total number of intervention groups	2
Each intervention group	CIMT
Specific intervention	2-hours of supervised intervention once every week for 8 weeks in a clinic Intervention by an OT (trained in CIMT by attendance at a 2-day workshop). Unaffected upper limb restrained for 2 hours each day with a custom made hand splint which prevented grasp Affected upper limb was engaged in usual, manipulative, fine motor activity (depending on age and ability).A guide for the activity was that it was achievable by the child. Caregivers used these sessions for ideas of how to continue at home for 2 hours each day for 6 days per week for the 8 week period.
Each interventon group	Control
Specific intervention	Neuro-developmental (NDT)(Conventional) therapy 2-hours each week for 8 weeks Included weight bearing and facilitation of arm movements based on the conventional NDT procedure. Therapists also visited the families at home once every week.
Outcomes	
Outcomes and time points	Assisting hand assessment (AHA) at 8 weeks from intervention start.
Outcome definition	Measures the effectiveness in which a child with unilateral disability aged between 18 months and 12 years uses his/her hand in assisting hand skills.
Unit of measurement	0-100 AHA units
Upper and lower limits and whether high or low score is good	0-100.High score is good
Results	
Number of participants allocated to each group	CIMT (7) Control (7)
Sample size	14 (7 in each group)
Missing participants	6
Baseline scores Mean (±SD)	AHA CIMT 41.6 (±12.6) Control 56.0 (±18.7)
Final value score immediately post intervention Mean (±SD)	AHA CIMT 48.0 (±11.7) Control 56.6 ± (18.7)
Estimate of effect (95%CI)	1.5
Key conclusions	CIMT group showed a good treatment effect
Study ID	**Fedrizzi et al., 2013**
Study design	Cluster randomised controlled trial
Study duration(weeks)	24
Randomisation (Group)	Randomisation at centre level. Procedure not reported.
Allocation concealment	Assessments were administered by a therapist and videotaped. Scoring was conducted from the tapes by a different therapist, blind to group allocation.
Blinding	Assessments conducted by blinded assessors
Other concerns about bias	Selection bias
Participants	
Total number	72
Setting	Rehabilitation centres
Diagnostic criteria	1) Hemiplegic cerebral palsy2) Aged between 2 and 8 years Excluded 1) If child had CIMT in the previous 6 months.2)injections of anti-spastic drugs

Interventions	
Total number of intervention groups	2
Each intervention group	CIMT
Specific intervention	2-hours of supervised intervention once every week for 8 weeks in a clinic Intervention by an OT (trained in CIMT by attendance at a 2-day workshop). Unaffected upper limb restrained for 2 hours each day with a custom made hand splint which prevented grasp Affected upper limb was engaged in usual, manipulative, fine motor activity (depending on age and ability).A guide for the activity was that it was achievable by the child. Caregivers used these sessions for ideas of how to continue at home for 2 hours each day for 6 days per week for the 8 week period.
Each intervention group	Control
Specific intervention	Neuro-developmental (NDT)(Conventional) therapy 2-hours each week for 8 weeks Included weight bearing and facilitation of arm movements based on the conventional NDT procedure. Therapists also visited the families at home once every week.
Outcomes	
Outcomes and time points	Assisting hand assessment (AHA) at 8 weeks from intervention start.
Outcome definition	Measures the effectiveness in which a child with unilateral disability aged between 18 months and 12 years uses his/her hand in assisting hand skills.
Unit of measurement	0-100 AHA units
Upper and lower limits and whether high or low score is good	0-100.High score is good
Results	
Number of participants allocated to each group	CIMT (7) Control (7)
Sample size	14 (7 in each group)
Missing participants	6
Baseline scores Mean (±SD)	AHA CIMT 41.6 (±12.6) Control 56 0(±18.7)
Final value score immediately post intervention Mean (±SD)	AHA CIMT 48.0 (±11.7) Control 56.6 ± (18.7)
Estimate of effect (95%CI)	1.5
Key conclusions	CIMT group showed a good treatment effect
Study ID	**Fedrizzi et al., 2013**
Study design	Cluster randomised controlled trial
Study duration(weeks)	24
Randomisation (Group)	Randomisation at centre level. Procedure not reported.
Allocation concealment	Assessments were administered by a therapist and videotaped. Scoring was conducted from the tapes by a different therapist, blind to group allocation.
Blinding	Assessments conducted by blinded assessors
Other concerns about bias	Selection bias
Participants	
Total number	72
Setting	Rehabilitation centres
Diagnostic criteria	1) Hemiplegic cerebral palsy2) Aged between 2 and 8 years Excluded 1) If child had CIMT in the previous 6 months.2)injections of anti-spastic drugs

Age Mean (±SD) Months	
Sex	36 boys 36 girls
Country	Italy
Co-morbidity	Cognitive clinical (20) CIMT(12) Control(8); Stereognosis alterations (6) CIMT(3) Control(3); Speech/language delay (16) CIMT(9) Control(7); Mood disturbance(10) CIMT(5) Control(5);Visual impairment (12)CIMT(10) Control(2);Visual attention disorder(7) CIMT(5) Control(2);Hearing impairment(1) CIMT(1) Control(0); Associated malformations(6) CIMT(6) Control(0) Epilepsy(6) CIMT(3) Control(3); Other co-morbidities(4) CIMT(4) Control(0);
Socio-demographic	
Ethnicity	Italian
Date of study	Recruitment ended in December 2008
Interventions	
Total number of intervention groups	3 (2 included)
Each intervention group	CIMT
Specific intervention	3 hours (divided into 1.5 hours with a therapist and 1.5 hours with the parent 3 times per week for ten-weeks Supervised sessions with the therapist and parent, At the rehabilitation centre, Unaffected hand was restrained for 3 hours per day with a fabric/plastic glove which prevented grasp Encouraged to perform tasks with the affected upper limb. This included holding and manipulative tasks and self-care activities such as drinking from a cup. Parents were trained to carry out similar 3-hour sessions at home on the remaining 4 –days and given a training booklet and DVD about the home programme.
Intervention group	Standard treatment
Specific intervention	One-hour of standard rehabilitation (40-60 minutes).The frequency depended on the child's age: infants (twice per week); pre-school and school age children (once per week).
Outcomes	
Outcomes and time-points	Quality of upper extremity skills test (QUEST) at ten-weeks post intervention start date.
Outcome definition	QUEST evaluates quality of upper extremity function in 4 domains: dissociated movement; grasp; protective extension and weight-bearing for children with neuromotor dysfunction aged 18 months to 8 years.
Unit of measurement	2 (able to complete item) 1(Unable to complete item 1(not-tested) Scores summed
Upper and lower limits and whether high or low score is good	0-100. High is good.
Outcomes and time-points	BESTA scale at ten-weeks
Outcome definition	Measures grasp and spontaneous hand use in play and activities of daily living
Unit of measurement	Ordinal scale from 3 sections A,B and C
Upper and lower limits and whether high or low score is good	Mean 0-3 (plus1) High score is good
Results	
Sample size	66
Number of participants allocated to each group	QUEST CIMT (39) Control (30)

	BESTA CIMT (39) Control (30)
Missing participants	3 (control group) 10% drop out from control group
Baseline scores. Mean (±SD)	QUEST CIMT 69.4 (±15.8) Control 72.2 (±17.2) BESTA Global CIMT 2.41 (±0.80) Control 2.71 (±0.79)
Final value scores immediately post-intervention. Mean (±SD)	QUEST CIMT 76.3 (±14.9) Control 72.6 (±17.7)
Final value scores immediately post-intervention Mean (±SD)	QUEST (grasp sub-score) CIMT 72.1(±18.8) Control 66.1 (±20.8)
Final value scores immediately post-intervention Mean (±SD)	BESTA Global CIMT 2.62 (±0.75) Control 2.68 (±0.71)
Final value scores immediately post-intervention Mean (±SD)	BESTA (grasp sub-score) CIMT 3.15(±0.66) Control 3.01(±0.78). (bimanual sub-score) CIMT 2.76(±0.88) Control 3.02 (±0.68) (ADL sub-score) CIMT 2.28 (±0.86) Control 2.43 (±0.98).
Estimate of effect (95%CI)	
Key conclusions	
Comments	A substantial improvement of the function of the affected upper limb in children treated with CIMT compared to standard treatment
Study ID	**Eliasson et al., 2011**
Study design	Crossover randomised controlled trial
Study duration(weeks)	32 (16 wash-out period)
Randomisation (sequence)	Sequence was produced using a computer-generated list of random numbers
Allocation concealment	The therapist who administered the assessment was not involved in the interventions. Video recording of the assessment was coded Therapist scoring the video did not know the child or the time of assessment.
Blinding	Video assessment scored by a blinded assessor
Other concerns about bias	Carry over effect between treatment sessions. Additionally, 24% drop-out.
Participants	
Total number	33
Setting	Home and pre-school setting
Diagnostic criteria	1)Hemiplegic cerebral palsy 2) Aged 18 months to 5 years 3) Ability to cooperate in the testing procedure 3) Parents willing to commit to 8 weeks intervention procedure Excluded 1)Visual or behavioral problems that would interfere with the testing or intervention 2) Had botulinum toxin in the upper limb in the last 6 months 3) Were included in another intensive training programme 4) Had undergone surgery or had another unstable medical situation during the study period
Age Mean (range). Months	CIMT 26.1 (20-32) Control 31.2(24-39) (Smania et al., 2009)
Sex	18 boys
Country	Sweden
Co-morbidity	
Socio-demographic	
Ethnicity	
Date of study	
Interventions	
Total number of intervention groups	2
Intervention group	CIMT
Specific intervention	2-hours intervention administered by parent or pre-school worker per day for 8 weeks Usual therapist visited once a week to plan and supervise the treatment In the child's usual environment (home or pre-school setting). Unaffected upper limb restrained with a fabric/plastic glove which

	prevents grasp Practiced activities with their affected hand designed by the therapist based on the results of the AHA.
Intervention group	Control
Specific intervention	Commonly, this was seeing an OT once per month and PT twice per month.
Outcomes	
Outcomes and time-points	Assisting hand assessment (AHA) 8 weeks from intervention start.
Outcome definition	Measures the effectiveness in which a child with unilateral disability aged between 18 months and 12 years uses his/her hand in assisting hand skills.
Unit of measurement	Scale 1-4 each item Summed to produce a total 0-100 AHA unit score
Upper and lower limits and whether high or low score is good	0-100. High score is good
Results	
Number of participants allocated to each group	CIMT(12) Control(13)
Sample size	25
Missing participants	CIMT(6) Control (2)
Baseline scores Mean (±SD)	AHA CIMT 53 (±10.0) Control 45 (±21.0)
Final value score immediately post-intervention Mean (±SD)	AHA CIMT 59 (±9.0) Control 46 (±21.0)
First treatment session	
Estimate of effect (95%CI)	5.47 (2.93-8.02)
Key conclusions	The ability to use the hemiplegic hand clearly improved after CIMT compared to the control period with a large effect size
Study ID	**(Smania et al., 2009)**
Study design	Crossover randomised controlled trial
Study duration (weeks)	19
Randomisation (sequence)	Procedure not described
Allocation concealment	Assessment videotaped and tapes scored
Blinding	Assessor was blinded to aim of study and group allocation
Other concerns about bias	Carry over effect between treatment sessions
Participants	
Total number	11
Setting	Outpatient rehabilitation centre
Diagnosis criteria	1) Hemiplegic cerebral palsy 2) Aged between 1 and 10 years 3)Mild-moderate motor disability only (able to reach and grasp a pellet) 4) Able to actively participate in the proposed activities 5) Good physical health Excluded 1)Severe behavioural problems2)Severe developmental delay3)Severe intellectual difficulties.
Age Mean (±SD). Months	57 (24)
Sex	7 boys 4 girls
Country	Italy
Co-morbidity	None
Ethnicity	Not reported
Date of study	Recruitment between Jan 2004-April 2006
Interventions	
Total number of intervention groups	2
Intervention group	CIMT
Specific intervention	1 hour twice each week of a supervised session with a physiotherapist (PT) for 5 weeks. Unaffected upper limb restrained for 8 hrs for 5 week period with a hand mitt which prevented grasp.

	Encouraged the child to repeat, self-generated activities of the affected hand that were at an appropriate level (Motor learning principle) During the session the therapist checked the child's hand activity and advised on how to progress the activities at home. Parents continued at home for 8 hours per day
Intervention group	Control
Specific intervention	Conventional PT One–hour twice weekly Child encouraged to repeat, self-generated activities of the affected hand that were at an appropriate level (Motor learning principle)
Outcomes	
Outcomes and time-points	Use test at 5 weeks post intervention start date.
Outcome definition	Spontaneous use of each arm during play (Study specific)
Unit of measurement	0= the arm was not used 1=the child tried to use the arm but unable to accomplish 2= the child used the arm successfully
Upper and lower limits and whether high or low score is good	0-64
Outcomes and time-points	Function test at 5 weeks post intervention start date.
Outcome definition	Bimanual function and affected and unaffected arm function (Study specific)
Unit of measurement	Bimanual function: 0= Not able to reach the ball 1= able to reach but not grasp the ball 2=reaches and grasps the ball with a lot of difficulty 3) = reaches and grasps the ball with minimal difficulty(score 0-24) Affected upper limb: 0=unable to accomplish the task 1= partial accomplishment of the task2) task accomplished with difficulty3) task accomplished with minimal difficulty (score =0-120) Unaffected upper limb: (same as affected (score =0-120))
Upper and lower limits and whether high or low score is good	0-264 High is good
Results	
Number of participants allocated to each group	Use test CIMT(5) Control(5) Function test CIMT(5) Control(5)
Sample size	10
Missing participants	1
Baseline scores Mean (±SD)	Not reported
Summary data. Mean change score from baseline Both treatment phases	CIMT group only reported. Use test: z score=2.652 p=0.008. Function test (Bimanual): z score=1.826 p=0.068. Function test (affected arm function): z score=2.371 p=0.018
Estimate of effect (95%CI)	
Key conclusions	Significant improvement of affected arm use and function and a trend toward bimanual function following CIMT
Study ID	**Abootalebi et al., 2010**
Study design	Randomised controlled trial
Study duration (weeks)	3
Randomisation (sequence)	Names written on a piece of paper and drawn out of a hat
Allocation concealment	Not described
Blinding	Not described
Other concerns about bias	

Participants	
Total number	12
Setting	
Diagnostic criteria	1) Hemiplegic cerebral palsy 2) Aged between 4 and 6 years 3) Wrist joint on the affected upper limb has >10 deg extension 4) Fingers on the affected upper limb have 10 deg extension 5) Able to grasp 6) Able to participate in activities. Exclusion: 1) Extremely retarded 2)Visual/hearing problem 3)History of orthopaedic surgery on the affected upper limb 4) Botulinum toxin in the last 6 months or awaiting injections
Age Mean (range). Months	59.91 (9.15)
Sex	5 boys 7 girls
Country	Iran
Co-morbidity	
Socio-demographic	
Ethnicity	
Date of study	
Interventions	
Total number of intervention groups	2
Intervention group	CIMT
Specific intervention	5 hours per day of OT 90% of waking hours for 21 consecutive days Unaffected upper limb restrained for 5 hrs in a sling Children participated in of occupational therapy
Intervention group	Control
Specific intervention	Routine therapy of 3 sessions each week for 45 minutes
Outcomes	
Outcomes and time-points 1) collected 2) reported	Peabody developmental motor scale (PDMS) at 3 weeks
Outcome definition	The PDMS is a standardised test, designed to evaluate both fine (FM) and gross motor (GM) skills in children from birth to 71 months of age. The PDMS-FM, consists of two subtests: Grasping, and Visual-Motor Integration
Unit of measurement	
Upper and lower limits and whether high or low score is good	The Fine Motor Quotient (FMQ) is derived by adding the subtest standard scores (score range: 1–20) and converting the sum to a quotient (range: 25–165).
Results	
Number of participants allocated to each group	CIMT(6) Control (6)
Sample size	12
Missing participants	
Baseline scores Mean (±SD)	CIMT 483.0 (54.04) Control Not reported
Final value score mean (±SD)	CIMT 528.8 (100.92) Control Not reported (p-value =0.069)
Estimate of effect (95%CI)	
Key conclusions	The use of CIMT did not significantly (p>0.05) improve the ability to use the affected upper limb more than usual therapy
Comments	
Study from the Cochrane systematic review (Hoare et al.,2007)	
Study ID	**Eliasson et al., 2005**
Study design	Clinical controlled cross-over trial
Study duration(weeks)	24
Randomisation (sequence)	No randomisation
Allocation concealment	Blind assessor not involved in interventions or data collection
Blinding	Assessor blinded to group allocation

Other concerns about bias	
Participants	
Total number	45 (25 CIMT) (20 Control)
Setting	
Diagnostic criteria	1) Hemiplegic cerebral palsy 2) Aged 18 mths-4 years Excluded:1) If could not understand simple commands.2) Nobody to carryout intervention at home/pre-school environment
Age Mean (±SD). Months	CIMT 28.8 (±8.2) Control 30.8 (±10.9)
Sex	20 boys 21 girls
Country	Sweden
Co-morbidity	Epilepsy (5) (CIMT(1) Control(4); Deaf (2) CIMT(1) Control(1) Both legs involved (2) CIMT(1) Control(1) Mild learning difficulty (1) CIMT(1) Control(0)
Socio-demographic	
Ethnicity	
Date of study	
Interventions	
Total number of intervention groups	2
Intervention group	CIMT
Specific intervention	2-hours per day for 8 weeks Therapist visited once a week to supervise the treatment Administered by the parent or pre-school worker In the child's usual environment (home or pre-school setting), daily. Unaffected upper limb restrained with a fabric/plastic glove which prevents grasp Practiced activities with their affected hand and based on principles motor learning The parents and pre-school workers attended an introductory seminar.
Intervention group	Control
Specific intervention	Commonly, this was seeing an OT once per month and PT twice per month General treatment within the paediatric service based on individual need. Consisted of teaching parents general stimulation of gross motor skills and monitoring of musculo-skeletal status
Outcomes	
Outcomes and time-points 1) collected 2) reported	Assisting hand assessment (AHA) at baseline and 8 weeks from intervention start.
Outcome definition	Measures the effectiveness in which a child with unilateral disability uses his/her hand in assisting hand skills
Unit of measurement	Scale 1-4 each item Summed to produce a Logit score
Upper and lower limits and whether high or low score is good	logit score:-10.26,8.72
Results	
Number of participants allocated to each group	21 (CIMT) 20 (Control)
Sample size	41
Missing participants	4 (CIMT)
Baseline scores Mean (±SD)	AHA CIMT -2.86 (±3.36) Control -2.23 (±3.14)
Final value score immediately post- intervention Mean (±SD)	AHA CIMT -1.63 (±2.91) Control -2.06 (±3.11)
Estimate of effect (95%CI)	1.16
Key conclusions	Children with hemiplegic cerebral palsy have been shown to benefit considerably more from a period of CIMT than those in the control group..

Interventions	
Total number of intervention groups	2
Each intervention group	CIMT
Specific intervention	2-hours of supervised intervention once every week for 8 weeks In a clinic Intervention by an OT (trained in CIMT by attendance at a 2-day workshop). Unaffected upper limb restrained for 2 hours each day with a custom made hand splint which prevented grasp Affected upper limb was engaged in usual, manipulative, fine motor activity (depending on age and ability).A guide for the activity was that it was achievable by the child. Caregivers used these sessions for ideas of how to continue at home for 2 hours each day for 6 days per week for the 8 week period.
Each intervention group	Control
Specific intervention	Neuro-developmental (NDT)(Conventional) therapy 2-hours each week for 8 weeks Included weight bearing and facilitation of arm movements based on the conventional NDT procedure. Therapists also visited the families at home once every week.
Outcomes	
Outcomes and time points	Assisting hand assessment (AHA) at 8 weeks from intervention start.
Outcome definition	Measures the effectiveness in which a child with unilateral disability aged between 18 months and 12 years uses his/her hand in assisting hand skills.
Unit of measurement	0-100 AHA units
Upper and lower limits and whether high or low score is good	0-100.High score is good
Results	
Number of participants allocated to each group	CIMT (7) Control (7)
Sample size	14 (7 in each group)
Missing participants	6
Baseline scores Mean (±SD)	AHA CIMT 41.6 (±12.6) Control 56 0(±18.7)
Final value score immediately post intervention Mean (±SD)	AHA CIMT 48.0 (±11.7) Control 56.6 ± (18.7)
Estimate of effect (95%CI)	1.5
Key conclusions	CIMT group showed a good treatment effect
Study ID	**Fedrizzi et al., 2013**
Study design	Cluster randomised controlled trial
Study duration(weeks)	24
Randomisation (Group)	Randomisation at centre level. Procedure not reported.
Allocation concealment	Assessments were administered by a therapist and videotaped. Scoring was conducted from the tapes by a different therapist, blind to group allocation.
Blinding	Assessments conducted by blinded assessors
Other concerns about bias	Selection bias
Participants	
Total number	72
Setting	Rehabilitation centres
Diagnostic criteria	1) Hemiplegic cerebral palsy2) Aged between 2 and 8 years Excluded 1) If child had CIMT in the previous 6 months.2)injections of anti-spastic drugs