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Disclosures:

This research project is supported by the Pierfranco e Luisa Mariani Foundation.

0894-9115/09/8803-0216/0
American Journal of Physical Medicine & Rehabilitation

DOI: 10.1097/PHM.0b013e3181951382

ORIGINAL RESEARCH ARTICLE

Multisite Trial on Efficacy of Constraint-Induced Movement Therapy in Children with Hemiplegia

Study Design and Methodology

ABSTRACT

Facchin P, Rosa-Rizzotto M, Turconi AC, Pagliano E, Fazzi E, Stortini M, Fedrizzi E, The Gipci Studi Group: Multisite trial on efficacy of constraint-induced movement therapy in children with hemiplegia: study design and methodology. Am J Phys Med Rehabil 2009;88:216–230.

Objective: In the past decades, several treatment approaches have been used to improve upper limb function in hemiplegic cerebral palsy. Only recently has constraint-induced movement therapy emerged as a treatment approach for children with hemiplegic cerebral palsy with the aim of reversing the behavioral suppression of movement in the affected upper limb. To date, evidence on this treatment has been very poor and limited, because all currently available trials reveal methodological limitations and a need for additional research to support the application of this treatment technique. This article presents the methodological choices, design, and main characteristics of an ongoing controlled clinical trial on the effectiveness and safety of constraint-induced movement therapy combined with an intensive rehabilitation program and compared with two comparison groups: one treated with an intensive rehabilitation program and the other with standard treatment.

Methods: Twenty-one rehabilitation sites are currently recruiting patients with hemiplegic cerebral palsy, aged between 2 and 8 yrs, who have never undergone constraint therapy. Primary outcome measures include two major domains: upper limb motor ability (Quality of Upper Extremity Skills Test) and hand function assessment evaluating both grip function and spontaneous use of the affected side (Besta scale). Secondary outcome measures concern overall function, behavior, compliance, and satisfaction with treatment program of both child and family. Patients' follow-up is of 12 mos after treatment.

Results: Research in children has always been neglected in comparison with adults, because of ethical reasons regarding the use of children for experimental purposes. The consequence has been the utilization of treatment and assessment tools and techniques that have not always been tested in pediatric patients or evidence is very scarce.

Conclusion: Discussing and working on pediatric research methods represents an urgent need in rehabilitation research.

Key Words: Hemiplegia, Cerebral Palsy, Constraint-Induced Movement Therapy, Outcomes

Hemiplegic cerebral palsy (CP) is the most common syndrome in children born at term, and it is second in frequency only to diplegia in preterm infants. In Italy, the incidence rate is 0.3–0.5/1000 newborns.[1,2]

Although almost all hemiplegic children achieve independent walking, impaired arm and hand function are the main problems in about half of the affected children,[3] particularly with regard to bimanual fine motor activity and reduced motor ability with increasing age. These factors contribute to disability in activities of daily living and everyday functional activities.[4]

During the past decade, considerable effort has been devoted to establishing novel approaches to overcome children's impairments and compromised ability to use their upper limbs to control and manipulate their environment.[5]

Several authors suggested that hemiplegic children learn to disregard the affected arm and tend to use their nonaffected arm as the dominant hand, even when functional loss is mild.[6] The term developmental disregard was introduced to describe all hemiplegic children disregarding and learning not to use the affected limb during their developmental motor function. This suggestion was confirmed by a follow-up study of functional outcome carried out on children with hemiplegic, whose results showed that hand function was better on request rather than during spontaneous use in bilateral manipulation.[4]

Several treatment approaches have been used to improve upper limb function in hemiplegic CP. A review conducted by Boyd et al.[5] listed different treatment modalities such as splinting, passive stretching, spasticity medication with baclofen and with botulin toxin A, and surgery.

More recently, a novel approach—constraint-induced movement therapy (CIMT)—based on the behavioral research conducted with nonhuman primates by Taub[7] in the 1980s—has been proposed. This therapy involves restraint of the nonaffected arm to encourage performance of therapeutic tasks with the affected arm, which children normally tend to disregard. CIMT has been used in several studies with adult populations presenting with different acquired conditions such as stroke, traumatic brain injury, and focal hand dystonia.[8] The results of the EXCITE [Extremity Constraint Induced Therapy Evaluation] trial recently published show significantly larger improvements in the group of patient undergoing CIMT both immediately after treatment and after 12 mos. The improvement regard quality and speed of paretic limb movement and amount of paretic arm use in activities of daily living.[9]

Evidence of Constraint Therapy in Children

Only recently has CIMT emerged as a treatment for children with hemiplegic CP with the aim of reversing the behavioral suppression of movement in the affected upper limb. According to a recently published Cochrane review,[10] evidence on this treatment is very poor and limited, because all currently available trials reveal methodological limitations and a need for additional research to support the application of this treatment. To date, three trials have been published in the international literature whose main characteristics are summarized in Table 1.[10,11]

The term CIMT describes an intervention that can be applied with numerous variants with regard to: method of restraint, length of restraint (per day, number of weeks), type and duration of therapy, intervention environment (home, school, or clinic), and intervention provider (therapist, parent or teacher).

As extensively underlined in the recent Cochrane review,[10] all currently available trials differ significantly in terms of methodological quality, sample sizes, treatment, and assessment tools. The first significant variant regard the method used to restrain the nonaffected limb: a broad range of techniques has been used from a glove or mitt,[12] to slings,[13,14] short-arm casts[15] and long-arm casts.[16] Second, treatment programs vary in intensity and typology, ranging from 2 mos of intervention 7 days per week,[16] 2 hrs per day[12] to twice weekly in 30 min-sessions for 6 wks.[15] Moreover, there is inconsistency in the length of time the child's nonaffected limb is restrained, varying from 6 hrs per day, all day,[15,16] for a period of 10 days[14] to 2 mos.[12] Furthermore, treatment programs range from no increase in routine occupational therapy or physiotherapy[15] to 8 hrs of therapy per day,[17] although there is currently no evidence that improvement is correlated to the time spent wearing the restraint during the treatment session.[12] The treatment setting can either be the home,[13,18] preschool,[12] a day camp,[19] the hospital or university clinic[20,21] or a combination of these environments. In general, all the settings described modulate differently the role and type of intervention required from parents or caregivers. Nonetheless, there is still insufficient support for the use of a specific device, technique or program.[10]

To date, treatment principles have been based on two different approaches, which vary according to the professionals involved[10]: on one hand, psychologists use the operant movement conditioning[14,16] and on the other, occupational therapists and physiotherapists adopt a motor learning and motor control approach, practicing repeatedly

TABLE 1 Currently available clinical trials on CIMT

Author	PY	Design	Methods	Participants	Interventions	Control group	Assessment tools	Cochrane review
Charles et al.[11]	2006	Randomized, controlled trial	Randomization. Blinding of 5 outcome assessors. Follow-up at 1 and 6 mos	*n*: 22 children Sex: 8 F, 14 M Mean age: 6 yrs 8 mos Range age: 4–8 yrs Diagnosis: hemiplegic CP Levels of severity: moderate	Type of constrain: use of a sling on the noninvolved upper limb for the entire time during an intervention session Treatment duration: 10 of 12 consecutive days during summer or school vacation, 6 hrs wearing the sling and 6 hrs with no sling Treatment setting: Columbia University Treatment program: individualized instructions from a trained interventionist involving specific practice of designated target movements. Children engaged in play and functional activities with 2 types of structured practice	Any treatment	Jebsen-Taylor test of hand function Bruininsk Oseretsky test of motor proficiency Caregiver functional use survey (CFUS) Hand-held dynamometer Modified Ashworth scale	No
Eliasson et al.[12]	2005	Controlled, clinical trial	No randomization. Blinding of outcome assessors. Follow-up at 2 and 6 mos	*n*: 45 children Treatment group: 21 control group: 20 Sex: 20 M, 21 F Age: 18–51 mos Diagnosis: hemiplegic CP Levels of severity: all	Type of constraint: use of a fabric glove with a built in stiff volar plastic splint on the "dominant" unaffected hand, preventing finger flexion and thumb movement Treatment duration: 2 mos of intervention 7 days per week, 2 hrs per day, which could be split into different sessions Treatment setting: child's usual environment (home/pre-school); therapist supervision once weekly Treatment programme: principles of motor learning, knowledge of motor control, with activities of an appropriate level of difficulty, and repetition	Traditional services	Assisting hand assessment (AHA)	Yes
Sung et al.[15]	2005	Randomized, controlled trial with no blinding of assessors	Follow-up at 6 wks.	*n*: 31 children Treatment group: 18 Control group: 13 Sex: 15 M, 16 F Age: <8 yrs Diagnosis: hemiplegic CP Levels of severity: mild, medium	Type of constraint: application of a short-arm Scotchcast from below the elbow to the fingertips on the unaffected upper limb Treatment duration: twice weekly in 30-min session for 6 wks for both groups Treatment setting: hospital setting. Provided by an occupational therapist Treatment programme: individualized functional occupational therapy (OT), and activities of daily living	Traditional services	Box and blocks test Erhardt developmental prehension assessment WeeFIM	Yes

TABLE 1 Continued

Author	PY	Design	Methods	Participants	Interventions	Control group	Assessment tools	Cochrane review
					Type of constraint: involved limb casted from upper arm to fingertips with lightweight bivalved fiberglass cast Treatment duration: 6 hrs per day for 21 days Treatment setting: hospital setting			
Taub et al.[16]	2004	Single blind, randomized, controlled crossover trial with blinding of Child Arm Use Test assessors	Follow-up at 3 and 6 wks and 3 and 6 mos (CIMT group only).	*n*: 18 children Treatment group: 9 Control group: 9 Sex: 13 M, 5 F Age: 7–96 mos (mean 41.5 mos) Diagnosis hemiplegic CP Levels of severity: all	Treatment programme: child behavior shaping, presenting activities to the child in ways that provided immediate, frequent, and repetitive rewards for the child's efforts and increasingly functional use of the more-impaired limb	Traditional services	Quality of upper extremity skills test (QUEST) Child arm use test (CAUT) Pediatric motor activity log (PMAL) Emerging behaviors scale (EBS)	Yes

highly motivating tasks.[12] This difference could be another variant of CIMT, although Taub and Wolf[22] suggested that the impact on CIMT outcomes is probably related more to intensity of treatment than to the treatment principle itself.

Although limited information is currently available on this issue, children's response to treatment may also be influenced by age, diagnosis, severity of motor and sensory impairment, comorbidities, presence and impact of mirror movements, cognitive abilities, and behavior.[10,12]

The clinical significance of study results so far is unclear also because of the lack of valid and reliable tools to measure the outcome, particularly the functional use of the hemiplegic hand in bimanual tasks.[10,12]

Another crucial point to be taken into consideration regard the treatment provided to comparison groups. In most cases no treatment or very basic treatment is provided, leading to a possible overestimation of the surplus value of CIMT (usually combined with an intensive rehabilitation program [IRP]) compared with other treatment options. In our opinion, this comparison does not allow to distinguish the costraint's effects from those of intensive rehabilitation and therefore assess the real effectiveness of constraint therapy.

The past published randomized, controlled trial[11] raises the question of whether similar intensive practices can be elicited without the restraint and whether this might result in even better functional results. This hypothesis was recently supported by Gordon et al.[23] who published a randomized trial demonstrating that bimanual intensive treatment results in a better outcome if compared with no treatment.

Nonetheless, results of currently available clinical studies have poorly contributed to estimate the effectiveness of CIMT in CP, also because of small study sample size resulting in inadequate power to detect statistical difference between the groups compared.[10]

Aim of the Study

These considerations have led us to a key question: is it possible to overcome these methodological problems and design a trial that can give strong evidence on CIMT effect? The aim of this study is to present the methodological choices, design, and main characteristics of a controlled clinical trial that is currently ongoing and whose recruitment is still open (although some patients have already completed the whole follow-up phase). The trial aims to study the effectiveness and safety of CIMT (defined as restraint combined with an IRP) compared with two comparison groups: one treated with an IRP and one with traditional treatment

Experimental Design

The study has been designed as a multicenter, prospective, controlled clinical trial on the efficacy of CIMT (consisting of the bandage of the unaffected arm with a specific device combined with a IRP for the affected arm) (group 1). At the end of the recruitment process, the results of this study group will be compared with those of two comparison groups, one undergoing bimanual IRP (group 2) and the other receiving traditional rehabilitation program (group 3). Recruitment of groups 1, 2, and 3 is currently ongoing and treatment programs are carried out in the same intervention period.

CIMT comprehends two major therapeutic elements, the restraint of the nonaffected limb and the massive practice of movements of the affected limb. The comparisons between groups 1 and 2 may highlight the effect of restraint and the comparisons between groups 1 and 3 and groups 2 and 3 may show the effect of massive practice of movements.

The traditional rehabilitation treatment (defined in the next paragraph) has been considered as the baseline treatment, allowing us to estimate if there is a surplus value in providing intensive treatment and which children would benefit the most.

Because of possible organizational difficulties within the rehabilitation services and the subsequent impossibility to randomize patients by treatment group in every single clinical center, the authors have chosen a cluster randomization design,[24,25] i.e., typology of trials in which groups or clusters rather than individuals are randomly allocated to different treatments. Cluster randomized trials are increasingly being used in the evaluation of healthcare interventions and the methodology for analyzing cluster randomization trials has been rapidly developing in the past decade.[26,27]

A crucial measure is the intracluster correlation coefficient. This coefficient measures the degree of similarity among responses to treatment within a cluster.[28] If we consider two hypothetical extreme situations, we can trace two different scenarios as follows:

1. The variability in treatment response is null within the clusters and maximum among the clusters: in this case clusters could be considered as a single individual for the trial; and
2. The variability in treatment response within the clusters and among the clusters are similar: in this case, the individuals are randomly distributed in the clusters and the statistical power randomizing the clusters is similar to the one obtained by randomizing individuals.

The measure identifying this "cluster effect" is inflation factor, the ratio between intracluster variability and intercluster variability of treatment effect outcome measure.[28]

Because it is very difficult to obtain accurate estimation of intracluster correlation, we have used a range of hypothesis to estimate intracluster coefficient, in order estimate the sample size and the power of the trial.[29]

To verify if the individuals were randomly distributed within the clusters, we used the IF of the main covariates such as age, severity of impairment, intelligence quotient, and parents' education level. No significant differences among variabilities of interclusters and intraclusters were observed in children enrolled in the trial.

Sample Size and Power

After the second hypothesis previously described, with a delta value set at 30%, (1 − [*beta*] = 0.80, [*alpha*] = 0.05, $\pi i = 0.15$), we estimated a sample to be recruited of 111 participants, considering a 10% dropout.

If at the end of the trial the intracluster correlation would be much higher than expected, the trial will be still valid but with a lower power and an [*alpha*] error tending to a constant value.[29]

Thirty-seven cases have been enrolled in 7 centers for CIMT, 37 cases in 7 centers for IRP and 37 case in 7 centers for traditional treatment.

Statistical Analysis

The effect of intervention will be assessed using a generalized estimation equation, an extension of logistic regression.[28]

Inclusion and Exclusion Criteria

Patient inclusion criteria are age range between 2 and 8 yrs, diagnosis of hemiplegic CP (anamnestic, clinical, and neuroimaging documentation to be collected) according to the classification of Hagberg et al.[30] To avoid the confounding effects of other intervention studies, potential participants have been or will be excluded from the study if they have previously undergone restraint therapy or have received or will receive injections of antispasticity drugs into upper limb musculature (e.g., botox). Differing clinical severity or comorbidity with other diseases (e.g., epilepsy, mental retardation . . .) or both do not constitute an exclusion criterion, but have been used to describe clinical variability.

Participants' motor criteria are divided into three groups as follows: (1) mild, (2) moderate, and (3) severe motor impairment, based on and modified from criteria set by Beckung and Hagberg[31] and Eliasson et al.[32] Operational definitions of degrees of severity were set as shown in Table 2.

Before starting the research program, all potentially eligible patients and their families have been or will be fully informed about the trial and

TABLE 2 Levels of severity of UE motor impairment

Group I	The paretic hand manipulates without restrictions but with limitations in more advanced fine motor skills
Group II	The paretic hand has only holding function during bimanual manipulation
Group III	The paretic hand has no functional ability

TABLE 3 Recruited patients: Baseline demographic information (collected with a dedicated recruitment questionnaire (Table 7)

Variable	Distribution
Age yr	
Average	4 yrs 8 mos
Range	2–7
Gender %	
Male	43
Female	42
Level of severity %	
I	52
II	39
III	9

treatments and if assenting, have been or will be asked to express a formal written consent

Participating Centers

Twenty-one clinical sites located in eight Italian regions take part in this research project. At least two clinicians per center are involved in the research project, a physician (neuro-pediatrician or physiatrist) and a physiotherapist. All the centers involved in the research study belong to the Italian group of CP (G.intraperitoneal C.I.), which was founded in 1994 and is composed of physiotherapists, physicians, and psychologists. The group has worked for 15 yrs in defining the decision-making process and clinical management of children with CP.

When the recruitment process will be completed, two supervisors of outcome measures will examine videotapes of all evaluations of patients from each treatment group and they will be blinded to treatment allocation.

Before commencing the trial, a steering committee composed of the principal investigator of each clinical site and the Data Management Center (DMC) made decisions relating to the study conduct. The DMC is located at the Epidemiology and Community Medicine Unit of the Pediatrics Department of Padua University. The DMC established a number of role-specific electronic mailing lists to facilitate communications among the various sites.

The present project was examined by an institutional review board that approved the study recommending to pay particular attention and care to the information given to families and children about the research program and treatment options, including the burden of the treatment program, the involvement of families, and the safety of treatment.

Baseline Information

Baseline information on each recruited patient is planned to be collected before commencing the trial: anamnestic and main clinical data, personal information, level of UE motor impairment severity, the presence of other diseases or disabilities or both (Annex 1). The data collected from patients recruited so far are summarized in Table 3.

Treatment Groups: Main Characteristics

Group 1. CIMT (Glove Plus Intensive Rehabilitation Program)

Children are to wear a restraining but fairly comfortable fabric glove with a built-in volar stiff plastic splint on the dominant hand, which prevents them from flexing their fingers and, thereby prevents the ability to grasp (Fig. 1). The thumb is kept in a fixed position tight against the index finger. The children can, however, use the hand for support or for breaking a fall. The intervention is planned to last 10 wks, 7 days a week. Children are expected to wear the glove for 3 hrs a day consecutively. During this interval, the child is expected to perform the therapeutic training under the supervision of the therapist or parents or both and without removing the glove.

During the treatment period, children undergo an IRP based on unimanual activities. They are treated for hand impairment according to a

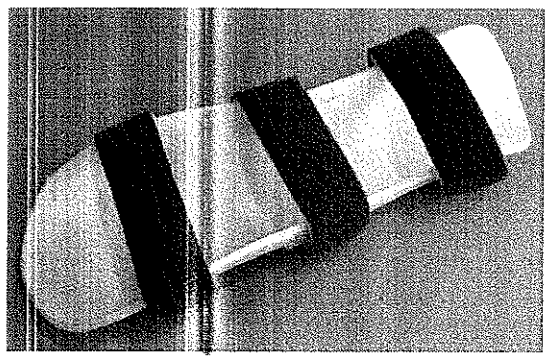

FIGURE 1 *Restraint glove utilized in CIMT group.*

motor learning approach during play sessions and activity of daily living. Sessions are held three times weekly at the rehabilitation center: an individual therapist encourages the child to solve tasks requiring the unilateral use of the paretic hand. Task goals refer to four main domains as follows: (1) perceptual motor activities; (2) activities of reaching, grasping, holding, and manipulating; (3) postural and balance activities; (4) self-care and daily living activities (Table 4).

Sessions are planned to last 3 hrs: during the first part of the session (1½ hrs) the therapist interacts with the child proposing unimanual activities of an appropriate level of difficulty, in relation to age and motivation. In the second part of the session (1½ hrs) parents, who cooperate during all the 3-hr sessions, are instructed to interact with their own children by proposing them unilateral tasks in play and daily living activities. Parents are trained to carry out similar 3-hr sessions at home on the remaining 4 days, as showed at the rehabilitation center (specific unilateral tasks during play and daily living activities).

Group 2. Bimanual Intensive Rehabilitation Program (IRP)

Children are treated for hand impairment according to the same approach described above, and with the same schedule (3 hrs a day, three times a week, half sessions with the therapist and half sessions with the parents) at the rehabilitation center: the only differences are that children do not wear the glove and are encouraged to solve tasks requiring the use of both hands.

Parents are trained to carry out similar 3-hr sessions at home on the remaining 4 days, as showed at the rehabilitation center (specific bimanual tasks during play and daily living activities).

Task goals refer to the same four main developmental domains, but they imply a bimanual use in play and daily living activities (Table 5).

Group 3. Traditional Treatment

This group includes children affected by CP currently treated in territorial rehabilitation services. They usually undergo 1-hr standard rehabil-

TABLE 4 Unimanual activities (CIMT group)

Domain	Repetitive Activities	Whole Task Practice	Elicited Movements
Perceptual motor tasks	Blind objects search and recognition Tactile exploration of different materials and surfaces, objects with different weight and consistency Pattern recognition of drawings traced on the palm of the affected hand	Nonstructured play activities. Examples 2–3 yrs (plasticine); 4–6 yrs (wheat cream); 7–8 yrs (pasta, rice)	Stereognosis adaptive grasp, finger singolaritation grasp, fingers singolarization, supination
Holding and manipulative tasks	Activities targeted to: string, lift, move get, and throw objects of different dimensions and shapes	Structured play activities. Examples 2–3 yrs [drawing; painting (finger paints)]; 4–6 yrs (puzzles, Lego building); 7–8 yrs (memory cards)	Wrist extension, finger singolarization release, thumb opposition
Posture and balance	Grab and carry small objects from/to different places and levels (high, low, front back up down)	Movement games. Examples 2–3 yrs (play ball); 4–6 yrs (play skittles); 7–8 yrs (play bowls and darts)	Shoulder flexion and abduction wrist extension, prono-supination forearm
Self-care and ADL		Examples 2–3 yrs (drink with the glass, smear face with cream or soap); 4–6 yrs (comb or brush hair; brush teeth); 7–8 yrs (spoon or fork use, dust a surface)	Precision grip, adaptive grip release, prono-supination

TABLE 5 Bimanual activities (control group 1)

Domain	Repetitive Activities	Whole Task Practice	Elicited Movement of Affected Hand	Evoked Use
Perceptual motor task	Fill up/empty big bottles or containers with wheat, rice, pasta, water, etc	Nonstructured play activities. Examples, 2–3 yrs (smear both upper limbs with cream, soap, or color); 4–6 yrs (paint palm and fingers of the affected hand with the other hand and make handprints); 7–8 yrs (play wind or percussion instruments)	Perceptive exploration, supination precision grip, release, finger singolaritation	Cooperation in bimanual task as assisting hand for holding and manipulation
Holding and manipulative tasks	Several symmetrical and asymmetrical activities (cork and uncork bottles, take off/put on top on marking pens, tear a piece of paper cut out a picture etc.)	Structured play activities. Examples, 2–3 yrs (playing dolls, drawing, painting); 4–6 yrs (Lego blocks); 7–8 yrs (puzzle, packaging, do the washing, spread out the washing, ironing linen, make pizza, cut fruits for food salad)	Adaptive grip, supination, release, bimanual coordination	Cooperation in bimanual task as assisting hand for holding and manipulation
Posture and balance	Grab and carry big objects from/to different places and levels (high, low, front, back, up, down)	Movement games. Examples, 2–3 yrs (play with a big ball); 4–6 yrs (tricycle, pull a chart); 7–8 yrs (play basket, bicycle)	Shoulder flexion, abduction, wrist extension and supination, bimanual coordination	Cooperation in bimanual task as assisting hand for holding and manipulation
Self-care		Examples, 2–3 yrs (drink with a big cup, break bread or sweets, wash hands and face); 4–6 yrs (take off the shoes and socks); 7–8 yrs (take off the shoes and socks, cooperate in bimanual ADL such as bring the plates, fold napkins, dry up kitchenware)	Adaptive grip, prono-supination, release, bimanual coordination	Cooperation in bimanual task as assisting hand for holding and manipulation

itation sessions once or twice a week and the session frequency differs in relation to child's age. Infants receive physiotherapy, mainly a neurodevelopmental treatment twice a week, whereas preschool and school-aged children attend occupational therapy once a week (40–60 mins).

Primary Outcome Measurements

During the five evaluation sessions (one before and one after the treatment program and three follow-up evaluations at 3, 6, 12 mos after treatment), primary outcomes are assessed in two major domains: upper limb motor ability (Quality of Upper Extremity Skills Test [QUEST[33]]) and hand function assessment evaluating both grip function and the spontaneous use of the affected side (Besta scale[4])

QUEST is an international validated scale exploring four main domains as follows: dissociated movement, grasp, protective extension, and weight bearing. The dissociated movement domain includes items that counter typical patterns of spastic synergy, representing each joint of the upper limb. Grasp items are based on normal hand grasps as described in developmental literature, arranged in a hierarchical and developmental framework. Weight bearing and protective extension are based on normal developmental sequence and are scored hierarchically based on the degree of abnormality as represented by joint positions. All items are scored for both arms using a dichotomous scale and percentage scores are calculated.[34]

The Besta scale is an instrument that was developed in 1985 at the Developmental Neurology Division of the Istituto Neurologico (Neurological Institute) "Carlo Besta" in Milan, to assess quality of grip (hand function on request) and spontaneous hand use (bilateral manipulation), and their changes in relation to age and degree of impairment. The first version of this assessment protocol was described in 1986, in a study in which clinical characteristics were analyzed in relation to etiologic factors and computed tomography findings in 30 children with congenital hemiplegia.[35] After modification, the instrument was used in a prospective study to evaluate changes in hand impairment and bilateral manipulation skills over time.[36] The interrater reliability was assessed with a pilot study conducted on 15 children with hemiplegia under 7 yrs of age and 15 children with hemiplegia over 7 yrs of age. Interobserver agreement of grip scores was excellent.[4]

In the scale, grip assessment is performed in a standardized setting, asking the child to pick up different sized cubes on request. The quality of grip is videotaped and scored in a hierarchical way (from 0 to 3). Spontaneous use is assessed during structured activities requiring both hands and being standardized according to age. The scoring system for the quality of manipulation is based on variability and stereotypy of movement pattern[37]: score 0, no use of impaired limb; score 1, use of impaired limb in a stereotyped pattern (wrist support) for holding; score 2, cooperation of the impaired hand in manipulation by holding with a restricted number of stereotyped patterns; score 3, cooperation of the impaired hand with holding and manipulation, using a varied repertoire of patterns.[4]

During the evaluation sessions, both tests are administered, video-recorded, scored on subsequent viewing, and videotapes are to be posted to the DMC for quality evaluation control.

Secondary Outcome Measurements

Besides the general assessment of patients (anamnesis, objective and neurologic examinations), evaluation sessions include additional tests assessing as follows: (a) the patients' cognitive level with the Wechsler/Griffiths scales (according to patient age), (b) general motor development with the gross motor function measure, (c) the level of familial stress with the Parenting Stress Index,[38] (d) parents evaluation of the child's autonomy in daily living activities using the Parents Besta Scale,[4] (e) the child behavior checklist,[39] and (f) treatment satisfaction and compliance perceived by parents using an ad hoc scale.

The purpose of including these other instruments in the evaluation sessions is to assess the child's overall development and if it is influenced by the treatment assigned.

The timing of secondary outcome measures evaluation is described in Figure 2 and Table 6.

Safety Measures

To evaluate the safety of the interventions carried out, the following measures have been used:

- Because the use of a restraint in the nonaffected limb could cause a motor impairment (as some studies on animal models have assumed[40]) and compromise the nonaffected-side ability, the function of the nonaffected limb is monitored through the QUEST and Besta Scales;
- Another parameter is the behavioral change in the child, that is assessed using the child behavior checklist. This scale can detect sudden modifications of child behavior, mood, or response to stress during and after the restraint of the nonaffected limb. The child behavior checklist[39] was designed to address the problem of defining child behavior problems empirically. It is based on a careful review of the literature and carefully conducted empirical studies. It is designed to assess in a standardized

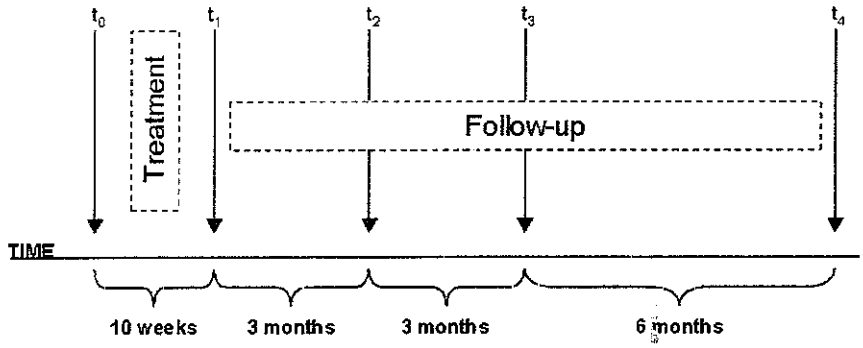

FIGURE 2 *Outcome measures evaluation scheme and timing*

format the behavioral problems and social competencies of children as reported by parents;
- Performing intensive treatment lasting 3 hrs a day per 10 wks can load on family life and increase the level of family stress. This evidence is evaluated through Parenting Stress Index.[38]

TABLE 6 Assessment protocol

Timing	Assessment Tools/Outcome Measures
t_0 (baseline)	Anamnesis/objective examination
	Neurologic examination
	Wechsler/Griffiths
	Gross motor function measure
	Parenting Stress Index
	QUEST
	Besta scale
	Besta scale for parents
t_1	Anamnesis/objective examination
	Neurologic examination
	Gross motor function measure
	Parenting Stress Index
	Child behavior checklist
	Treatment satisfaction and compliance scale
	QUEST
	Besta scale
	Besta scale for parents
t_2	Anamnesis/objective examination
	Neurologic examination
	Gross motor function measure
	Child behavior checklist
	QUEST
	Besta scale
	Besta scale for parents
t_3	Anamnesis/objective examination
	Neurologic examination
	Gross motor function measure
	QUEST
	Besta scale
	Besta scale for parents
t_4	Anamnesis/objective examination
	Neurologic examination
	Gross motor function measure
	QUEST
	Besta scale
	Besta scale for parents

Baseline, Post-Immediate, and Follow-Up Evaluations

The timeline for baseline, post-treatment/control period, and follow-up evaluations is outlined in Figure 2 and Table 6. Only primary outcomes are evaluated at each evaluation visit. Evaluation visits are planned at baseline, end of treatment, and after 3, 6, and 12. The study plan provides that the follow-up ends at month 14.5 from the baseline date.

Training, Standardization, and Agreement

Before starting the controlled trial, a specific training program was provided to familiarize pro-

TABLE 7 Baseline information collected per each eligible case

Rehabilitation center
Patient initials
Date of birth
Sex
Gestational age
Side of hemiplegia
Age of onset: mos
Level of severity
Plausibile pre/perinatal cause or acquired cause
Cognitive disturbances
Stereognosis alterations
Speech/language delay
Mood disturbances
Visual impairment
Visual attention disorders
Hearing impairment
Associated malformations
Skeletal
Visceral
Presence of epilepsy
Other comorbidities
MRI results (leucomalacia, cerebral malformation, other cerebral alterations)
CT scan; ultrasound, SPECT results

fessionals with testing and training procedures to develop a homogeneous administration and videotaping of the QUEST and Besta Scale tests, as well as the parents of recruited children.

Professionals—Principal Investigator

First of all, the principal investigators of the participating centers were equipped with a training package including a presentation module illustrating the sections of each scale (QUEST and Besta Scale) and describing the scoring procedures with practical video-recorded examples, which included the videos of three children with different levels of hemiplegia, two of which were scored and the third was blind (with the scoring enclosed in a sealed envelope).

After the self-training phase, a meeting with scale experts was organized for the principal investigators to discuss issues related to administration: recording procedure and scoring process.

The project included an assessors' agreement phase. The main goal of this phase was represented not only by the need of providing a standardized training for all assessors, but also to be able to measure the variability of primary outcome measures to use this coefficient as an estimation of the variability of the "instrument of measure" of primary endpoint. Each clinical centre provided the video-recording of the administration of the 2 tests (QUEST and Besta Scale) to 2 children of their hemiplegic population, in all 42 cases (2 per each centre) who undergone the administration and video-recording of 2 tests; in all 84 videos, 42 Besta scale and 42 QUEST scale). The coordinating centre sent the 84 videos to all the 21 participating centre and all videos were scored by the principal investigator (a total amount of 84 assessments, 2 per all 42 children video-recorded). All evaluations were collected and analyzed by the coordinating centre to evaluate the agreement among the investigators involved, considering separately in the analysis each item scored, partial scoring values of scales sections and total scoring values of Besta and QUEST scales.

Two training core members of staff evaluated the videotapes to assess the quality of procedures used by each clinical center and exclude participants that were not sufficiently trained, and they also rated the videotapes.

Periodical meetings were held during the second project year among all the representatives of the participating centers. These meetings included participant chart reviews, focus groups with research participants, and key informative interviews with training core staff. Information gathered during these meetings, along with data collected with the standardization procedures, was included in a trial evaluation process.

Professionals—Therapists

All the therapists involved in the trial belong to the G.intraperitoneal C.I. group and they are trained to use the same motor learning approach during play and activities of daily living since 15 yrs. All therapists involved in the treatment development have been trained and equipped with a manual listing the theoretical framework of rehabilitation programs to be carried out and many practical examples of activities and tasks (both unimanual and bimanual) to be developed during the treatment sessions. The manual had a DVD attached showing some examples and activities. New personnel employed were trained in the same way. Nevertheless, to further standardize the administration of the therapeutic training, all the therapists of the participating centers had several meetings to verify the standardization of therapeutic procedures among the therapists through practical activities with simulated and real cases. Tables 4 and 5 show the theoretical framework and some practical examples of activities and tasks of experimental treatment.

Parents

The activities and tasks proposed and developed during the intensive treatment sessions were shown and taught to parents that are asked to attend all the treatment sessions. The family compliance to the suggestions given by the therapist during the treatment sessions was verified periodically and, in the recruitment phase, the family undertook to develop all the activities at home for the duration required. The compliance was an essential requirement for the child recruitment in the clinical trial. Moreover, a manual and several videos showing the therapeutic activities were published and handed out to families to equip parents with an instrument to carry out the activities at home during play and daily living.

Standardization

On what attains the assessment procedures the standardization was guaranteed by the following:

1. Strict timing in tests administration during the trial, constantly verified by the DMC;
2. Common training period for the scales administration and video-recording procedure;
3. Analysis of interobserver variability through the interscorer agreement;
4. Mandatory videorecording of the administration scales monitoring primary endpoint (Besta and QUEST) for all the trial assessment phases; and
5. Evaluation of two expert external supervisors of all the videos recorded during the trial and the

agreement phases blinded to treatment allocation.

On what attains the treatment procedures the standardization was guaranteed by the following:

1. The 15-yr belonging to a common working group on CP (G intraperitoneal C I), sharing a practical and theoretical framework of all therapists;
2. Clear and detailed definition of the treatment programs of the three groups specified for age classes;
3. Pretrial common training period for the treatment procedure for all the therapists involved in the study;
4. Two manuals + DVD for therapists and for parents showing some examples of training activities and tasks both in the rehabilitation center setting and at home; and
5. Mandatory participation of the parents to the treatment sessions at the rehabilitation center to learn the activities and tasks to be repeated at home.

DISCUSSION

Clinicians involved in rehabilitation agree on the need for scientifically credible evidence, which shows that interventions are safe, effective, and worthwhile. In the past decade, research in the field of rehabilitation has been increasingly interested in randomized clinical trials as the preferred design for outcome studies. Nevertheless, in medical rehabilitation the design and conduct of randomized clinical trials imply many challenges. Among the others, Fuhrer[41] mentioned the following: (a) difficulties in blinding the administrators of interventions or the recipients; (b) resistance of candidate participants to being randomly assigned to experimental or control groups; (c) the unacceptability, ethically or otherwise, of using control conditions that withhold or delay treatment; (d) the extreme complexity of some interventions that makes it difficult to monitor the fidelity with which they are administered; (e) an insufficiency of eligible participants in any one setting, necessitating difficult to administer, multisite trials; and (f) the relatively lengthy follow-up interval of some rehabilitation trials that makes them vulnerable to participant attrition.

In pediatric rehabilitation, other challenges are to be added, such as the overlap between intervention effects and natural process of function development, and the marked variability of the clinical picture among participants of different ages and the degree of functional impairment. Moreover, in infancy and childhood, the biological evidence of many developmental disorders is still very poor and therefore it is often very difficult to define the "rationale" of assessment and treatment methodology.

In the field of hemiplegic CP another challenge is represented by its rarity (0.3–0.5/1000 Italian newborns[1,2]) and therefore by the difficulty to collect large samples of participants for research programs. Moreover, assessment tools of upper limb function which is the principal goal of the rehabilitation treatment in this form of CP, are very few, and mainly derive from adult protocols.

How can these problems be tackled and managed when designing a trial on the efficacy and safety of CIMT in hemiplegic children? The Cochrane review recently analyzed several clinical aspects of three trials on CIMT in children with hemiplegic, namely the method of constraint frequency and intensity of practice, intervention environment and social context, intervention principles, individual characteristics of children, and outcome measures.[10] All these aspects varied significantly in the three trials published[8,12,15] particularly in relation to intensity of treatment. Moreover, the samples of children were very small, lowering the power of the studies. Finally, in our opinion, the comparison between children treated with a combination of constraint of the nonaffected hand and intensive practice of the affected hand, and children not treated at all is not correct, because it does not allow to distinguish between the effect to be attributed to the restraint and that to be attributed to the intensity of treatment, thus presumably overestimating the effect of CIMT.

For all these reasons, it is very difficult to assess the real efficacy of CIMT itself. In fact, although the results of Eliasson et al.[12] did not support its efficacy, Taub and Wolf[22] had previously formulated the hypothesis that the intensity and not the principle of treatment could have an impact on outcomes. The randomized clinical trial results published by Gordon et al[23] on the efficacy of a hand-arm bimanual intensive therapy in hemiplegic children seem to confirm this idea, i.e., the efficacy of intensive treatment alone would improve bimanual hand use and elicited practice rather than restraint may be responsible for improved motor performance. These encouraging results on small samples of patients need to be urgently confirmed by studies on larger samples of cases, to have enough power to exclude the null hypothesis and give clear significant results that do not need further investigation. For this reason, our study has chosen to enroll 37 patients per group, for a total amount of 111 patients.

To overcome many of the problems posed by conducting a trial in the domain of pediatric rehabilitation such as the need to collect large samples, the GIPCI group chose to conduct the trial on

CIMT in hemiplegic children as a multisite clinical trial. According to Meinert,[42] a trial must possess three characteristics to be considered multiple site in nature. First, the data ought to be acquired from two or more settings that are organizationally independent. Second, a common intervention and data collection protocol ought to be used, and third, data management and analysis ought to be centralized. All these characteristics have been respected in the design of our research study.

As Fuhrer[43] suggested, the advantages of multisite trials are the collection of larger samples, the rapidity in study completion and enhancement of generalizability of findings. Our MSCT in fact involves 21 rehabilitation centers, most of them located in Northern Italy, which deal with the treatment of CP children in ordinary clinical practice. Therefore, this trial may have the advantage of giving a measure of the effectiveness of the treatment, and particularly of determining whether interventions have beneficial results in the real context where new cases with hemiplegic CP will have to be treated.[44]

However, multisite clinical trials are more challenging in terms of organization, management, and administration. The main problem concerns intervention fidelity that is the degree to which the essential features of experimental and control interventions are implemented and planned.

Another relevant aspect of this trial is the choice of outcome measures which is justified not only by the need for objective and reproducible measurements, but also by the usefulness of considering primary hand function outcomes as strictly related to secondary outcomes namely the child's overall development, familial environment and quality of life. This choice is based on the principle that any modification determined by a rehabilitation intervention is the result of a balance between changes in hand and limb function, global motor and cognitive development, and the child's quality of life. For example, this mutual influence can paradoxically result in a positive effect of the affected limb, but in a negative effect on overall motor development as demonstrated in animal models.[40]

The participation of many centers in our trial has raised several questions when planning the trial, particularly with regard to the practitioners' different experiences and skills, the diversity in treatment setting, the difference in the use of outcome measures.

To overcome these problems, 1 yr has been entirely dedicated to planning and implementing the study design and to training all the professionals (physicians and therapists) involved in the research project. The protocol features, including enrolment criteria, outcome measures, method of constraint, principles of treatment, intensive practice, and parent cooperation, have been specified, discussed, and explained, also with the use of videorecordings. In each center, a doctor is responsible for assessment and treatment fidelity and many meetings have been organized to verify the homogeneity of assessment and interventions. The interscorer agreement on the main outcome measures of upper limb function and the standardization of treatment practice were lengthy processes, but were worthwhile because they enhanced the practitioners' expertise and awareness. Another important innovation of this research study regard the deep involvement of parents in treatment sessions and their training to continue the exercises at home: their involvement plays a key role in the treatment program and in changing their attitude toward the value of treatment and the role of daily activities and actions in improving the use of the affected hand and their children's quality of life.

The effort of staff members involved in the research project is focused on monitoring the quality of protocol implementation over time, checking the experimental and control interventions carried out and introducing corrective factors, if necessary.

In conclusion, the planning and implementation of this multisite study on the safety and efficacy of CIMT in children with hemiplegic has so far achieved a first important goal besides defining the study design: it has increased the knowledge and expertise of many clinicians involved in pediatric rehabilitation with regard to research study methodologies and practices.

According to the authors of the review recently published by Cochrane,[10] "... given the paucity of evidence, the use of CIMT in children with cerebral palsy should still be considered experimental. Further adequately powered RCTs, using valid and reliable outcome measures, are required to explore the effectiveness of CIMT for children with hemiplegic cerebral palsy. Future research in CIMT should investigate the most efficient, cost-effective, least invasive, and family-friendly treatment protocol that can be easily replicated in a clinical setting."

As already stated, research in children has always been neglected in comparison with adults, because of ethical reasons regarding the use of children for experimental purposes. The consequence of this attitude has been the utilization of treatment and assessment tools and techniques whose efficacy has not yet been tested in pediatric patients or evidence is very scarce. The authors believe that discussing and working on pediatric research methods represents an urgent need in rehabilitation research.

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APPENDIX

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