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Implications of providing wrist-hand orthoses for children with cerebral palsy:

Evidence from a randomised controlled trial.

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Title

Implications of providing wrist-hand orthoses for children with cerebral palsy: Evidence from a randomised controlled trial.

Abstract

Purpose

To investigate the effects of providing rigid wrist-hand orthoses plus usual multidisciplinary care, on reducing hand impairments in children with cerebral palsy.

Methods

A pragmatic, multicentre, assessor-blinded randomised controlled trial aimed to enrol 194 children aged 5-15 years, with wrist flexor Modified Ashworth Scale score ≥1. Randomisation with concealed allocation was stratified by study site and passive wrist range. The treatment group received a rigid wrist-hand orthosis, to wear ≥6 hours per night for 3 years. Analysis included repeated measures mixed-effects linear regression models, using intention-to-treat principles.

Results

The trial stopped early due to insufficient recruitment: 74 children, across all Manual Ability Classification System levels, were randomised (n=38 orthosis group; n=36 control). Mean age was 10.2(SD 3.1) years (orthosis group) and 9.1(SD 2.8) years (control). Data showed some evidence that rigid wrist-hand orthosis impacted passive wrist extension with fingers extended in the first year [mean difference between-groups at 6 months: 13.15° (95%CI: 0.81° to 25.48°, p=0.04); 12 months: 20.94° (95%CI: 8.20° to 33.69°, p=0.001)]. Beyond 18 months, participant numbers were insufficient for conclusive findings.

Conclusion

The study provided detailed data about short- and long-term effects of the wrist-hand orthosis and highlighted challenges in conducting large randomised controlled trials with this population.

Trial Registration

Australia and New Zealand Clinical Trials Registry: U1111-1164-0572

Key words

Cerebral palsy, child, randomised controlled trial, range of movement, upper limb impairment,

Implications for rehabilitation

- There may be incremental benefit, for children with cerebral palsy, at 6 and 12 months on passive wrist range from wearing a rigid wrist-hand orthosis designed according to this protocol.
- The rigid-wrist-hand orthosis evaluated in this study, which allowed for some tailoring for individual children's presentations, differed in design from past recommendations for 'resting hand' positioning.
- Longitudinal follow up of children with cerebral palsy prescribed a rigid wrist-hand orthosis is essential to monitor any benefit.
- Minor adverse events were commonly experienced when wearing the orthosis and should be discussed prior to prescription of a rigid wrist-hand orthosis.

Introduction

Children with cerebral palsy (CP) present with movement disorders that place them at risk for developing secondary musculoskeletal impairment, including loss of range of movement, contractures and deformity (1, 2). Until recently, evidence about the longitudinal development of upper limb passive range of movement has been lacking. A population-based study of Swedish children with CP (n = 771) demonstrated that 34% had contractures of the upper limb and 20% of the wrist, with evidence that upper limb contracture starts prior to three years of age (3).

Conventional thought is that children with CP benefit from wearing wrist-hand orthoses (also called splints) to prevent muscle stiffness, loss of range of movement and development of contracture (4, 5). Current practice is variable based on geography, clinical (technical) expertise and resources (6). While wearing orthoses appears to do little harm, their benefits, indications for use or if they should be persisted with in all situations, are not known.

One reason for wrist-hand orthoses is to provide a sustained low-load stretch to the forearm muscles to counteract the effects of over-activity which result from spasticity/dystonia, and therefore to maintain or improve range of movement. Prolonged posturing in shortened muscle positions associated with muscle overactivity may contribute to failure of longitudinal muscle growth and increased resistance to passive stretch (1, 7, 8).

A systematic review about the effects of providing stretch interventions (including orthoses) to maintain or improve range of movement across a range of diagnostic groups in children and adults, demonstrated that stretch is not effective (9). Meta-analysis, with upper and lower limb muscle groups pooled across age groups, demonstrated a mean difference of 2° (95%CI: 0° to 3°) at short-term follow-up in people with neurological conditions (9). The applicability of Harvey et al.'s evidence for children with CP – whose contractures develop as they grow and

whose muscle structure may differ from adults with an acquired condition (10) – is also limited by the short intervention periods reported in the review (≤ 7 months) (9).

A systematic review (6) of the effects of orthoses for children with CP identified a lack of clarity about relationships between: (i) the intended aim of the orthosis; (ii) presumed mechanism(s) of effect; and (iii) outcome measures that connect aims with intended effects. The primary aim of this pragmatic trial was to evaluate whether the medium to long-term use (i.e., 3 years) of rigid wrist-hand orthoses (rigid-WHO) combined with usual multi-disciplinary care with children with CP aged 5 years or older, could prevent or reduce loss of range of movement, compared to usual multi-disciplinary care alone. The impact of orthoses on muscle stiffness/tone, pain, activity performance and improved ease of care for families was evaluated.

The trial was prospectively registered on the Australian and New Zealand Clinical Trials Registry (ANZCTR): U1111-1164-0572 and the protocol published (11). The trial stopped early due to insufficient recruitment. The purpose of this paper, therefore, is to report what was learned about the effect of the intervention and consider implications for future practice and research.

Research objectives

The original research questions (11) were amended to reflect changes due to insufficient recruitment and few participants with data collected at 3-years, which precluded the intended superiority approach to analysis. The revised research objectives were to explore if a rigid-WHO combined with usual multi-disciplinary care, compared to usual multi-disciplinary care alone;

1. improved passive range of movement or prevented further loss of movement at the wrist (wrist extension measured with fingers extended) across the duration of the study; and

2. changed the development of muscle stiffness, pain, activity performance, ease of care, participation and quality of life outcomes, across the duration of the study.

We also aimed to examine if an interaction existed between age or severity and provision of a rigid-WHO in combination with usual multi-disciplinary care, compared to usual multi-disciplinary care alone, in reducing or preventing further development of muscle stiffness and pain, and improving activity performance and/or ease of care at three years from baseline.

Methods

The methods detailed in the published protocol (11) are summarised here, and protocol deviations reported.

Design

A pragmatic, multicentre, assessor-blinded randomised controlled trial with 1:1 allocation to rigid-WHO intervention or control group was employed. Participants were assessed every 6 months for 3 years or until the trial ceased. Using a parallel group design, we tested the effect of intervention in the context of usual multidisciplinary care. An economic evaluation was embedded in the trial and is reported separately (12).

Ethical approvals and governance

Ethical and/or governance approvals were received from Monash Children's Hospital Human Research Ethics Committee (HREC: 14199B) and The Royal Children's Hospital (HREC: 34280A) in Victoria, Cerebral Palsy Alliance in NSW (HREC: 214-08-02), Perth Children's Hospital in Western Australia (HREC: 2014060), Deakin University (HREC: 2016-231) and Australian Catholic University (HREC: 2014 317 V). Gaining consent involved providing parents or guardians and eligible children with written information about the study, and an in-

person discussion with study personnel which included information about the aims, the implications of randomisation, and any potential risks or benefits of taking part. Written consent was obtained from parents or guardians and children provided assent where possible.

Participants and recruitment

Participants were recruited from five sites in Australia. Eligible children were diagnosed with CP, aged 5-15 years at time of recruitment and presented with Modified Ashworth Scale (MAS) (13) score ≥1 in wrist flexors, tested during wrist extension with fingers extended. Children had one or both upper limbs included based on each wrist meeting eligibility criteria. Excluded were children who: (i) had upper limb surgery within the past 12 months; (ii) presented with dystonia without spasticity; (iii) were allergic or sensitive to orthosis materials; or (iv) were unable to access a study site. Also excluded were children whose parents expressed concerns about their ability to undertake the intervention and those who were unable to understand written English - as resources for translation of study materials were not available. We recruited therapists who fabricated rigid-WHOs for included children and obtained information about their professional background and experience.

The sample estimate (97 children per group) was calculated for the primary outcome of passive range of wrist extension with fingers extended to detect a 10º between-group difference of passive range of movement at 3 years. Recruitment used multiple and repeated site-specific strategies and continued for 2.5 years (mid-2015 to end-2017).

Randomisation

Independent, concealed randomisation to group was completed using a secure REDCap-based (14) procedure. An independent statistician generated the randomisation list of randomly

permuted blocks of length 2, 4, and 6, with allocation stratified by study site (5 strata based on location) and passive wrist range (3 strata: wrist extension with fingers extended > 0°; wrist extension with fingers extended between -45° and 0°; or wrist extension with or without fingers extended < -45°, where possible range was approximately minus 90° to plus 90°). Limbs of children with bilateral presentation where both wrists met the inclusion criteria were randomised to the same group.

Interventions

All children received the multidisciplinary care their parents and health care teams deemed appropriate. This included any form of upper limb intervention (e.g., bimanual therapy, constraint-induced movement therapy, or botulinum toxin-A injections), and daytime orthoses which were intended to support children to use their hands more effectively during daily activities. The only difference between groups was the provision of orthoses in the rigid-WHO group.

Rigid wrist hand orthosis group

Children in the rigid-WHO group received a custom-made orthosis designed to maintain wrist, fingers and thumb flexors in a lengthened position to avoid shortening of the musculo-tendinous unit and other soft tissues and mobilise tissue by passively applying forces to gain motion (6). Therapists fabricated and monitored orthoses according to consensus-based guidelines developed by study investigators. The guidelines comprised a set of principles to guide positioning of the wrist, fingers and thumb, based on the child's available range and the relative contribution of wrist and finger flexor stiffness (see (11)). Serial adjustment, or a new fabrication, of the orthosis was undertaken as needed during the study. To achieve a prolonged stretch, orthoses were to be

worn for a minimum of 6 hours (typically overnight) for each 24-hour period for the study duration.

To monitor fidelity of orthosis prescription, pairs of occupational therapist investigators independently reviewed photographs of fitted orthoses for adherence to the fabrication guidelines. If necessary, fabricating therapists were advised about adjusting fit to meet the guidelines.

Control group

Children in the control group received usual multidisciplinary care and were asked to refrain from wearing a rigid-WHO for the study duration.

Intervention modification protocol

Wrist range of movement and muscle stiffness were monitored in both groups 6-monthly. Given the natural history of CP can include loss of range of movement and the intended trial length, the trial protocol allowed for children assessed after the first 12 months who experienced a loss of passive range of wrist extension of ≥30° or an increase in wrist MAS score of ≥2 categories compared to baseline, in either group, to be provided with: (a) review of measures to check for errors; (b) increased frequency of monitoring to 3 monthly; (c) serial casting if deemed clinically appropriate; and/or (d) referral for a surgical opinion.

Monitoring concomitant interventions

Rigid-WHO use and concomitant therapy were monitored using TherApp or a paper-based diary, and a 6-monthly study-specific questionnaire. TherApp sent a daily prompt (text) to children's parents in the rigid-WHO group to record time the orthosis was worn each 24-hour period. Once per week, TherApp prompted parents of children in both groups to identify upper limb therapy

provided that week. The 6-monthly study-specific questionnaire collected frequency and reason for attendance at specialist services, frequency of participating in upper limb therapies and details about medications for management of muscle overactivity.

Data collection

Clinical data were collected by trained assessors who were blinded to children's group allocation. Reliability of primary outcomes – wrist range of movement and MAS – was checked, and training continued until differences between assessors at each trial site were <5° or ≤1 category on the MAS. In six cases, an error in data collection of wrist extension at baseline was detected. Additional assessor training and system prompts were implemented to address the potential for systematic errors in data collection.

Demographic data were collected at baseline and included sex, age, associated conditions, functional classification of gross motor, manual ability, communication and bimanual function, type of movement disorder, and topographical distribution.

Outcomes measured

Outcome measures assessed variables across International Classification of Functioning Disability and Health (ICF) domains (15). Body structure and function measures were collected, by an assessor blind to group allocation, 6-monthly, activity level measures annually, and quality of life and participation measures at baseline and 3 years (or at child's final visit before trial cessation).

Body structure and function measures were: goniometric measures of passive range of wrist extension (fingers extended/fingers flexed), supination and elbow extension; active range of wrist extension; MAS (13) and Modified Tardieu Scales (16) (finger flexors, wrist flexors,

forearm pronators and elbow flexors); grip strength (dynamometer); Neurological Hand Deformity Classification (NHDC) (17); House Thumb in Palm (18); and hand/arm pain.

Activity-level measures were the Pediatric Evaluation of Disability Inventory – Computer Adaptive Test Self-care domain (19); ABILHAND-Kids (20); Box and Blocks Test (21); and ease of caregiving. Participation measures were the Participation and Environment Measure for Children and Youth (22) and quality of life was measured using the CP Quality of Life Questionnaire (23) and the Child Health Utility-9D (24). Supplementary Table 1 displays details of measures.

Monitoring harms and adverse events

Parents of children in the rigid-WHO group received a weekly TherApp prompt to provide information regarding fit, comfort or adverse events. Six-monthly study-specific questionnaires collected adverse events for all children.

Statistical methods

Statistical analysis included all randomised participants where outcome data were available, and participants were analysed according to the group to which they were randomised. All analyses were conducted in Stata 16.1. The statistical analysis plan is available online at https://doi.org/10.25374/MCRI.16968379.

The primary outcome (passive range of wrist extension with fingers extended) was summarised and graphically presented as means and SDs at each time point (6, 12, 18, 24, 30 and 36 months). As primary analysis, the comparison between rigid-WHO and control groups is presented as the mean difference (MD) and its 95% confidence interval (CI) at each timepoint, obtained using a repeated measures two level mixed model. This mixed-effects linear regression model included:

random intercepts for limb and for child, and fixed effects for: treatment group, time of assessment, treatment-time interaction, stratification factors used in randomisation (site and wrist range of movement category), age at baseline (continuous), outcome measure at baseline, hand severity at baseline (severe levels vs not severe levels, as measured by NHDC), and Bimanual Fine Motor Function (BFMF) (25) at baseline. As secondary analysis on the primary outcome, a further mixed-effects linear regression model was run that included the same random effects listed above, and only the stratification factors used in the randomisation as fixed effects. To explore evidence for an interaction between age at baseline and treatment, as well as for an interaction between hand deformity severity at baseline and treatment, two further separate mixed-effects linear regression models included a fixed effect of the interaction term age-treatment and a fixed effect of the interaction term NHDC-treatment.

We only report results from the fully adjusted analyses as these provide more precise estimates of the treatment effects on the outcomes. The adjusted mean differences were calculated using the Stata command `xtmixed`, with specification of treatment group (arm), time of assessment (time), treatment-time interaction, site (psn_pt1) and wrist range of movement category (stratum), age at baseline (age_t0), outcome measure at baseline (outcome_t0), hand severity at baseline (nhdc_t0), and Bimanual Fine Motor Function (bfmf_t0) at baseline in the fixed effects part [*fe_equation*] of the syntax and limb (limb_id) and child (study_id) in the random effects [*re_equation*] part.

(full syntax used `xtmixed outcome i.arm##i.time i.stratum i.psn_pt1 c.outcome_t0 i.nhdc_t0 c.age_t0 i.bfmf_t0 || study_id: || limb_id: time , var reml).`

As there was no evidence of interaction effects between baseline age or severity and outcomes, these results are not presented. Since baseline passive range of wrist extension with fingers extended (primary outcome) was incorrectly assessed at one site for six children, a sensitivity analysis was run that excluded these children's baseline primary outcome measures. Findings were consistent with the primary results and are not presented.

Continuous secondary outcomes are reported as mean and SD at each time point by treatment group and were analysed using the same mixed-effects linear regression model used for primary analysis of the primary outcome. Categorical secondary outcomes are presented as number and proportion in each category by group, as are the incidence of harm and adverse events.

We interpret the strength of the evidence obtained from inferential analyses as weak (large *p-values*, close to 1.0), strong (small *p-values,* less than ~0.001), or as providing 'some' evidence against the null hypothesis, with increasing strength as the *p-value* becomes smaller (26, 27). We interpret the clinical importance of differences between groups in the primary outcome as being ≥10° of wrist extension with fingers extended, in accordance with the effect size used *a priori* to determine the sample size.

Results

Participant recruitment and characteristics

Of those who took part in a conversation about the study, and/or were screened for eligibility (n=338), 74 (22%) provided informed consent and were randomised (n = 38 rigid-WHO; n = 36 control). See Figure 1 for flow of participants through the trial.

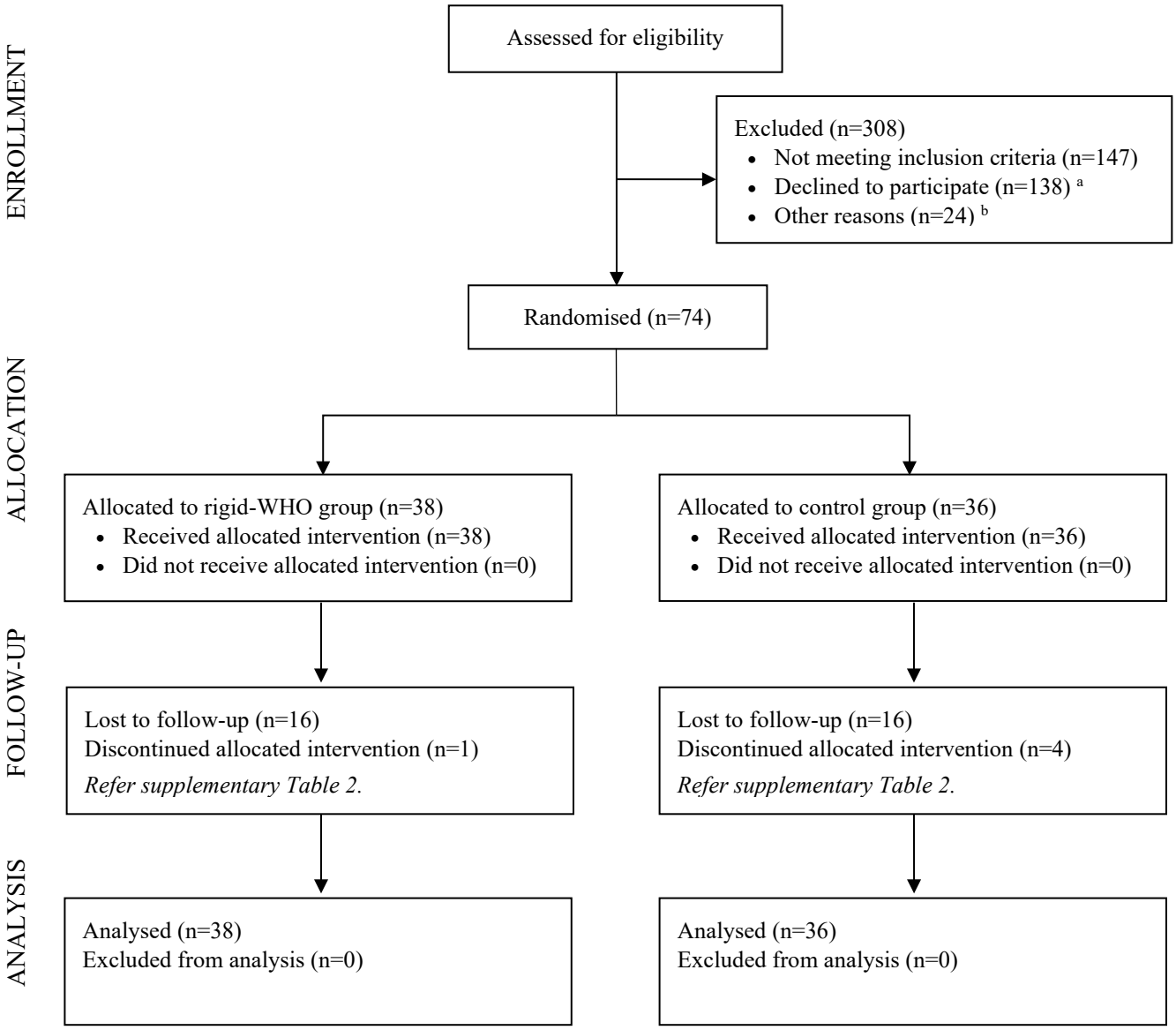

Figure 1. Consort flow diagram.
Note: Because recruitment strategies varied across sites, data about numbers of parents/children who received study information is not possible to report. [a] Declined: Insufficient time (n=18); Not interested (n=58); Belief rigid-WHO not required, would not benefit and/or be tolerated (n=29); Not wishing to give up existing rigid-WHO if randomised to control group (n=30); Not wish to attend assessments (n=3). [b] Verbal consent not converted to written consent for reasons: trial ceased before baseline (n=4); lost contact with family (n=19); unable to obtain foster-authority consent (n=1). Rigid-WHO = rigid wrist-hand orthosis intervention.

Figure 1. Alt Text: Flow diagram shows numbers of participants assessed for eligibility to take part in the study (n=382), reasons for not being eligible, numbers allocated to the rigid-WHO (n=38) and control groups (n=36), and those included in the analyses (all allocated).

Baseline participant characteristics are displayed in Table 1. Of the 74 recruited participants, 54% were female, 36.5% had bilateral presentation of their movement disorder and there were participants classified at each level of the Manual Ability Classification System (MACS) (28). Consistent with population characteristics (3), 50% of the sample was classified at MACS levels I or II. A disproportionate number, however, were classified at MACS levels I (5.4%) and II (44.6%), in comparison with Swedish population data suggesting 35% and 22% respectively. Groups were similar at baseline on the MACS, Gross Motor Function Classification System (GMFCS) (29), the Communication Function Classification System (CFCS) (30) and the BMFM (24). About 42% presented with both spasticity and dystonic posturing of the included limb.

Participants' mean study duration was 18.1 (SD 10.6) months in the rigid-WHO group and 19.3 (SD 11.1) in the control group. Five participants (n=3 rigid-WHO, n=2 control) reached the 36-month assessment prior to trial cessation (Supplementary Table 2 – participant withdrawals and duration in the study). In addition to stopping early, there were ten protocol deviations involving eight participants, and one control-group participant received casting in response to loss of passive range of wrist extension of ≥30° (Supplementary Table 3 – protocol deviations and intervention modifications). Participants in both groups received a range of upper limb therapies (Supplementary Table 4 – concomitant upper limb therapies).

Table 1. Baseline characteristics of participants.

Participants	**Rigid-WHO Group N=38**	**Control Group N=36**
Limbs included	47	49
With co-existing dystonia	19/47 (40.4%)	22/49 (44.9%)
Sites		
Cerebral Palsy Alliance (NSW)	7 (18.4%)	6 (16.7%)
Perth Children's Hospital (WA)	17 (44.7%)	16 (44.4%)
Ability Centre (WA)	1 (2.6%)	0 (0.0%)
Monash Children's Hospital (VIC)	7 (18.4%)	9 (25.0%)

Royal Children's Hospital (VIC)	6 (15.8%)	5 (13.9%)
Wrist extension		
> 0	33 (86.8%)	32 (88.9%)
≥ -45 to ≤0	4 (10.5%)	2 (5.6%)
< -45	1 (2.6%)	2 (5.6%)
Age (years; Mean (SD))	10.2 (3.1)	9.4 (2.4)
Sex:		
Male	18 (47.4%)	16 (44.4%)
Female	20 (52.6%)	20 (55.6%)
Unilateral/Bilateral CP		
Unilateral	26 (68.4%)	21 (58.3%)
Bilateral	12 (31.6%)	15 (41.7%)
Limbs included in the study		
Right only	18 (47.4%)	13 (36.1%)
Left only	11 (28.9%)	10 (27.8%)
Both	9 (23.7%)	13 (36.1%)
Right limb included	27 (71.1%)	26 (72.2%)
With dystonia	13/27 (48.1)	11/26 (42.3)
Left limb included	20 (52.6%)	23 (63.9%)
With dystonia	6/20 (30.0)	11/23 (47.8)
Bimanual Fine Motor Function (BFMF)		
Level I	2 (5.9%)	6 (20.0%)
Level IIa	22 (64.7%)	17 (56.7%)
Level IIb	1 (2.9%)	0 (0.0%)
Level IIIa	2 (5.9%)	1 (3.3%)
Level IIIb	4 (11.8%)	2 (6.7%)
Level IVa	1 (2.9%)	2 (6.7%)
Level V	2 (5.9%)	2 (6.7%)
Manual Ability Classification System (MACS):		
Level I	2 (5.3%)	2 (5.6%)
Level II	16 (42.1%)	17 (47.2%)
Level III	9 (23.7%)	7 (19.4%)
Level IV	5 (13.2%)	3 (8.3%)
Level V	6 (15.8%)	7 (19.4%)
Gross Motor Function Classification System (GMFCS)		
Level I	13 (34.2%)	11 (30.6%)
Level II	12 (31.6%)	12 (33.3%)
Level III	1 (2.6%)	1 (2.8%)
Level IV	4 (10.5%)	4 (11.1%)
Level V	8 (21.1%)	8 (22.2%)
Communication Function Classification System (CFCS)		
Level I	16 (42.1%)	19 (52.8%)
Level II	11 (28.9%)	8 (22.2%)
Level III	2 (5.3%)	4 (11.1%)
Level IV	6 (15.8%)	3 (8.3%)
Level V	3 (7.9%)	2 (5.6%)

Note: Age range of total sample at baseline: 5.1 to 15.0 years; [a] missing data n = 4 rigid-WHO, n = 6 control.

Intervention fidelity and adherence

The 12 therapists who fabricated orthoses were occupational therapists with 3-19 years of paediatric neurology experience (see Supplementary Table 5). Data on fidelity of rigid-WHO fabrication were available for 35 (92%) children at baseline (including 42 limbs), and 23 occasions when a replacement orthosis was required. Of the 61 rigid-WHO reviewed, 49% (n = 31) were volar and 51% (n=32) were dorsal/volar. Supplementary Table 6 displays data on adherence to the rigid-WHO guidelines and fabrication materials used in Supplementary Table 7.

Technical difficulties with TherApp and reliability of paper-based reporting resulted in significant missing data for monitoring adherence to orthosis use and concomitant interventions. Data on rigid-WHO use, was available for an average of 50.6% of the days that participants were in the study (i.e., data were missing for 49.4% of days). On average, rigid-WHOs were known to be worn 27.8% (SD 22.9%) of days; not worn 9.6% (SD 9.7%); and it was unknown whether the rigid-WHO was worn on 13.2% (SD 26.8%) of days participants were in the study and had data available (see Supplementary Table 8). When worn, the mean hours of wearing were 7.5 (SD2.4) (see Supplementary Table 9).

Adverse events and risks of harm

TherApp data on adverse events were available for 34 (89%) participants in the rigid-WHO group. Due to interruptions in TherApp functioning, data may under-represent the frequency of orthosis-related events. Twenty-four (63%) participants experienced at least one mild orthosis-related adverse event of short duration (median 1 week; IQR 1, 2 weeks; see Table 2). One serious and two moderate events were reported, each unrelated to the rigid-WHO.

Table 2. Mild adverse events reported via the TherApp for children in the rigid-WHO group.

	No. of times event reported n (%)	No. of children experiencing event n (%) N=34	Discrete[a] occurrences per child median [IQR] min-max	Duration of event (consecutive weeks) median [IQR] min-max
Events <u>related</u> to rigid-WHO	**295**	**24/34 (71)**		
Related to rigid-WHO fit	**106/295 (36)**	**14/24 (58)** [b]		
Skin redness, irritation or rash	70/106 (66)	12/14 (86)	1 [1,3] 1-12	1 [1,2] 1-4
Blister	7/106 (7)	3/14 (21)	1 [1,2] 1-2	1 [1,1] 1-2
Bruising	4/106 (4)	2/14 (14)	1 [1,1] 1-1	1 [1,2] 1-2
Swelling	3/106 (3)	2/14 (14)	1 occurrence	1 wk; 2 wks
Other	22/106 (21) [c]	8/14 (57)	1 [1,4] 1-5	1 [1,2] 1-2
Related to rigid-WHO wear	**189/295 (64)**	**18/24 (75)** [b]		
Sleep disturbance	95/189 (50)	11/18 (61)	3 [2,3] 1-14	1 [1-2] 1-12
Behaviour disturbance	31/189 (16)	5/18 (28)	3 [1,10] 1-15	1 [1,1] 1-3
Pain not related to above symptoms	63/189 (33)	12/18 (67)	1 [1,3] 1-6	1 [1-3] 1-10
Events <u>unrelated</u> to rigid-WHO [d]	**7**	**2**		

Note: [a] A discrete occurrence is defined as the same event being reported by the same participant across consecutive weeks. [b] Frequencies and percentages may not add up as the same child may have experienced more than one type of adverse event. [c] Other events related to rigid-WHO fit included: cast/splint too tight/small (n=9); sweaty hand/wrist (n=4); skin infection (n=4); losing grip of pencils, toothbrush (n=2); nil details provided (n=1); hit self with splint causing blood nose (n=1); child says arm getting cold, but not (n=1). [d] Adhoc reporting of adverse events unrelated to rigid-WHO included: unwell (n=4); chest infection (n=2); Hand, foot and mouth disease (n=1).

Primary and secondary outcomes

Table 3 displays the results on the primary and secondary outcomes for body function and activity. There was some evidence in favour of rigid-WHO on the primary outcome of passive wrist extension with fingers extended at 6 months (adjusted mean difference (adj-MD) 13.15°; 95%CI 0.81 to 25.48; p=0.04) and 12 months (adj-MD 20.94°; 95%CI 8.20 to 33.69; p=0.001). Adjusted mean differences at both these time points were >10°, our criteria for a clinically

important difference. The evidence weakened at 18 months [adj-MD 8.49° (95%CI: -5.66° to 22.63°, *p*=0.24)]. Beyond 18 months, participant numbers were insufficient to enable conclusive findings (see Figure 2a).

There was weak evidence (large *p*-values) about the effect of rigid-WHO on passive wrist extension with fingers flexed (see Figure 2b), and active wrist range of motion (see Figure 2c) at any time point. Differences were all <10°, except at 36 months, where sample sizes were n=4 (rigid-WHO) and n=3 (control), and at some timepoints the direction of effect favoured the controls. Reduced sample sizes beyond the 18 months timepoint provide insufficient power for interpretation of large differences at 36 months, which favoured control for the primary outcome and rigid-WHO for active range of movement. There was some evidence of effect of rigid-WHO on grip strength at 12 months (adj-MD 5.65 Newtons; 95%CI 0.88 to 10.41; *p*=0.02; see Figure 2d), but not at any other time point. There was weak evidence (large *p*-values) about the effect of rigid-WHO on pain, difficulty positioning the hand, and other activity level measures (Box and Blocks Test, ABILHANDS-Kids, Self-care domain of PEDI-CAT; see also Supplementary Figures 1 to 4).

Table 3. Body function and activity level outcomes.

	Rigid-WHO Group n, mean (SD) [missing]	**Control Group n, mean (SD) [missing]**	**Adjusted MD [a] 95%CI, p**
Passive range of motion (degrees) - Wrist extension (FE)			
Baseline	46, 52.4 (37.3) [1]	49, 60.4 (44.6) [0]	
6 months	38, 56.5 (31.0) [0]	37, 50.7 (50.1) [0]	13.15 (0.81 to 25.48) , p=0.04
12 months	36, 61.3 (33.1) [0]	36, 45.4 (49.8) [0]	20.94 (8.20 to 33.69) , p=0.001
18 months	26, 66.7 (31.4) [0]	33, 56.2 (48.4) [0]	8.49 (-5.66 to 22.63) , p=0.24
24 months	10, 79.7 (16.8) [0]	21, 69.3 (30.4) [1]	8.98 (-8.79 to 26.75) , p=0.32
30 months	8, 44.3 (48.4) [0]	10, 53.5 (44.6) [0]	2.36 (-21.15 to 25.87) , p=0.84
36 months	4, 65.8 (26.6) [0]	3, 29.7 (72.3) [0]	-35.90 (-82.99 to 11.19) , p=0.14

Passive range of motion (degrees) – Wrist extension (FF)			
Baseline	47, 73.0 (17.8) [0]	49, 72.2 (28.5) [0]	
6 months	38, 71.8 (22.0) [0]	37, 70.9 (33.0) [0]	2.13 (-3.93 to 8.20) , p=0.49
12 months	36, 73.4 (21.9) [0]	36, 67.8 (36.5) [0]	3.25 (-2.99 to 9.49) , p=0.31
18 months	26, 77.5 (24.7) [0]	33, 69.5 (36.2) [0]	4.50 (-2.33 to 11.34) , p=0.20
24 months	10, 83.9 (14.6) [0]	21, 81.7 (17.7) [1]	5.86 (-2.54 to 14.26) , p=0.17
30 months	8, 59.4 (39.1) [0]	10, 75.0 (19.1) [0]	3.55 (-7.18 to 14.28) , p=0.52
36 months	4, 77.8 (19.4) [0]	3, 67.0 (34.8) [0]	1.22 (-19.52 to 21.96) , p=0.91
Active range of motion (degrees) – Wrist extension (fingers extended) [c]			
Baseline	35, -2.3 (44.1) [12]	36, 13.9 (40.9) [13]	
6 months	28, 12.0 (39.8) [10]	29, 19.8 (38.1) [8]	-5.89 (-22.31 to 10.54) , p=0.48
12 months	28, 12.6 (46.3) [8]	28, 19.7 (39.5) [8]	-5.58 (-22.35 to 11.20) , p=0.51
18 months	22, 24.8 (33.7) [4]	23, 20.4 (42.1) [10]	7.37 (-10.96 to 25.70) , p=0.43
24 months	10, 17.0 (45.9) [0]	15, 28.7 (35.8) [7]	7.72 (-13.39 to 28.83) , p=0.47
30 months	6, 34.5 (46.3) [2]	6, 28.8 (33.5) [4]	5.15 (-23.11 to 33.40) , p=0.72
36 months	4, 23.3 (56.1) [0]	1, -10.0 (.) [2]	31.35 (-19.88 to 82.59) , p=0.23
Grip strength (Newtons)			
Baseline	35, 14.7 (16.2) [12]	39, 15.0 (15.9) [10]	
6 months	29, 17.6 (19.0) [9]	33, 13.8 (12.1) [4]	2.97 (-1.43 to 7.37) , p=0.19
12 months	28, 19.6 (23.2) [8]	26, 13.6 (11.6) [10]	5.65 (0.88 to 10.41) , p=0.02
18 months	19, 23.7 (28.4) [7]	23, 16.0 (14.1) [10]	3.29 (-2.22 to 8.80) , p=0.24
24 months	9, 24.0 (35.5) [1]	15, 20.1 (10.9) [7]	6.90 (-0.14 to 13.93) , p=0.05
30 months	6, 37.9 (38.5) [2]	6, 17.1 (8.5) [4]	1.36 (-8.17 to 10.89) , p=0.78
36 months	4, 41.6 (43.8) [0]	1, 8.7 (.) [2]	5.05 (-12.06 to 22.16) , p=0.56
Manual dexterity - Box and Blocks Test score			
Baseline	33, 12.6 (10.7) [14]	35, 12.5 (11.1) [14]	
6 months	No observations	No observations	
12 months	28, 14.9 (11.7) [8]	26, 17.1 (13.7) [10]	0.17 (-3.64 to 3.98) , p=0.93
18 months	6, 16.0 (9.5) [20]	6, 15.2 (17.1) [27]	4.64 (-1.49 to 10.77) , p=0.14
24 months	10, 16.7 (14.3) [0]	13, 22.8 (10.9) [9]	-1.33 (-6.21 to 3.55) , p=0.59
30 months	5, 15.8 (14.9) [3]	6, 19.3 (5.6) [4]	-6.38 (-13.48 to 0.73) , p=0.08
36 months	4, 17.8 (19.1) [0]	1, 18.0 (.) [2]	-7.81 (-18.52 to 2.90) , p=0.15
Manual ability - ABILHAND-Kids logit score			
Baseline	36, -0.6 (3.5) [2]	32, -0.5 (3.5) [4]	
6 months	No observations	No observations	
12 months	14, 0.3 (3.6) [15]	14, -0.1 (4.3) [12]	-0.06 (-1.81 to 1.70) , p=0.95
18 months	No observations	No observations	
24 months	1, -0.7 (.) [8]	5, 2.3 (2.7) [12]	-1.21 (-5.09 to 2.67) , p=0.54
30 months	No observations	No observations	
36 months	No observations	No observations	
Self-care skills - Daily Activities: PEDI-CAT score [d]			
Baseline	37, 50.5 (8.4) [1]	35, 49.7 (9.4) [1]	
6 months	No observations	No observations	
12 months	25, 51.3 (9.2) [4]	25, 50.7 (9.5) [1]	-0.15 (-1.93 to 1.64) , p=0.87
18 months	7, 49.9 (10.3) [13]	4, 46.5 (12.8) [20]	3.68 (-0.06 to 7.42) , p=0.05
24 months	8, 55.6 (7.8) [1]	11, 52.2 (7.3) [6]	1.14 (-1.42 to 3.70) , p=0.38
30 months	2, 60.0 (2.8) [5]	4, 49.0 (8.3) [3]	-0.04 (-4.43 to 4.35) , p=0.99
36 months	3, 55.0 (5.6) [0]	1, 42.0 (.) [1]	Not able to be estimated.
Difficulty in positioning hand or arm (0-10)			
Baseline	41, 6.1 (2.7) [6]	35, 4.1 (3.0) [14]	

6 months	10, 5.5 (2.8) [28]	15, 4.0 (2.4) [22]	1.78 (-0.55 to 4.11) , p=0.13
12 months	35, 5.1 (2.5) [1]	36, 4.8 (3.1) [0]	0.28 (-1.45 to 2.00) , p=0.75
18 months	12, 4.7 (3.4) [14]	6, 4.5 (2.7) [27]	0.90 (-2.36 to 4.15) , p=0.59
24 months	10, 4.2 (2.9) [0]	20, 4.5 (2.6) [2]	-1.21 (-3.36 to 0.94) , p=0.27
30 months	6, 5.2 (2.8) [2]	10, 5.9 (2.8) [0]	0.24 (-2.62 to 3.10) , p=0.87
36 months	4, 5.0 (2.4) [0]	3, 6.7 (1.2) [0]	-0.56 (-5.48 to 4.35) , p=0.82
Pain severity in the arm (0-10) [b]			
Baseline	11, 4.4 (2.5) [36]	10, 4.1 (2.2) [39]	
6 months	11, 3.9 (2.4) [27]	2, 2.5 (3.5) [35]	0.80 (-2.73 to 4.33) , p=0.66
12 months	11, 4.3 (2.9) [25]	7, 2.6 (2.6) [29]	2.24 (-0.19 to 4.67) , p=0.07
18 months	3, 6.0 (0.0) [23]	12, 4.3 (3.0) [21]	2.03 (-1.57 to 5.64) , p=0.27
24 months	1, 5.0 (.) [9]	1, 4.0 (.) [21]	1.23 (-4.71 to 7.17) , p=0.69
30 months	4, 4.5 (2.6) [4]	3, 3.0 (1.0) [7]	-1.15 (-5.13 to 2.83) , p=0.57
36 months	No observations	No observations	
Pain severity in the hand (0-10) [b]			
Baseline	12, 3.8 (1.9) [35]	9, 3.9 (2.4) [40]	
6 months	10, 3.8 (2.5) [28]	2, 4.0 (1.4) [35]	-1.52 (-4.34 to 1.30) , p=0.29
12 months	11, 3.8 (3.0) [25]	7, 1.6 (1.1) [29]	0.88 (-1.50 to 3.26) , p=0.47
18 months	3, 6.0 (0.0) [23]	12, 3.0 (2.3) [21]	2.74 (-0.38 to 5.87) , p=0.09
24 months	1, 5.0 (.) [9]	1, 1.0 (.) [21]	3.29 (-0.89 to 7.48) , p=0.12
30 months	4, 4.5 (2.6) [4]	2, 1.5 (2.1) [8]	0.19 (-5.34 to 5.72) , p=0.95
36 months	No observations	No observations	

Note: n = number of included limbs unless otherwise indicated. FE=fingers extended. FF=fingers flexed. [a] Adjusted MD derived from mixed-effects linear regression model which included the following baseline factors: age, corresponding outcome measure, Neurological Hand Deformity Classification and Bimanual Fine Motor Function, plus site and wrist range of movement category, time of assessment, treatment-time interaction and random intercepts for the limb and for the child. [b] Only adjusted for stratification factors used in randomisation. [c] Active range of motion measured three times on each occasion and highest value recorded. [d] Sample size for PEDI-CAT is number of participants. (.) value could not be calculated

Figure 2a. Passive wrist extension with fingers extended.

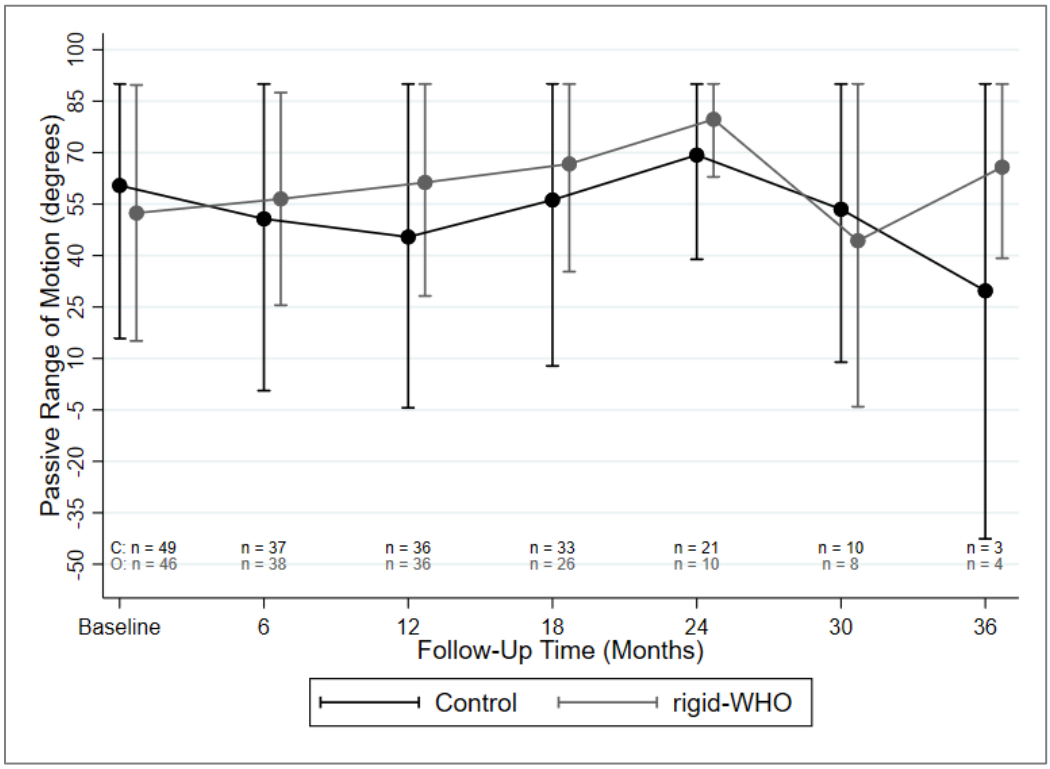

Figure 2b. Passive wrist extension with fingers flexed.

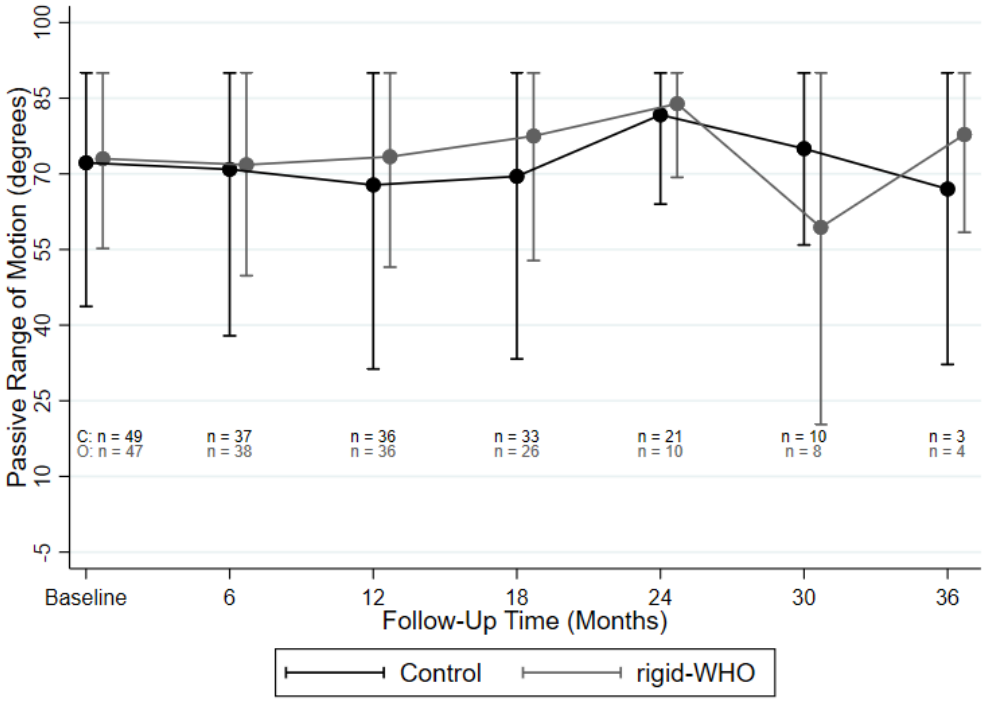

Figure 2c. Active wrist extension with fingers extended.

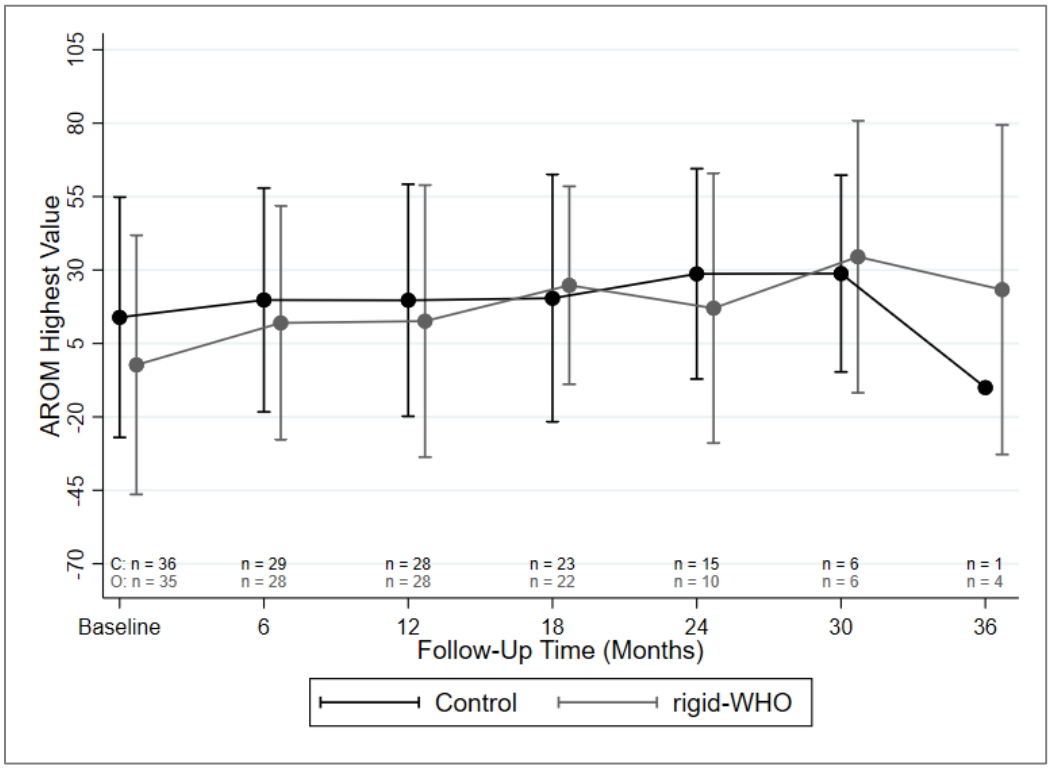

Figure 2d. Grip strength.

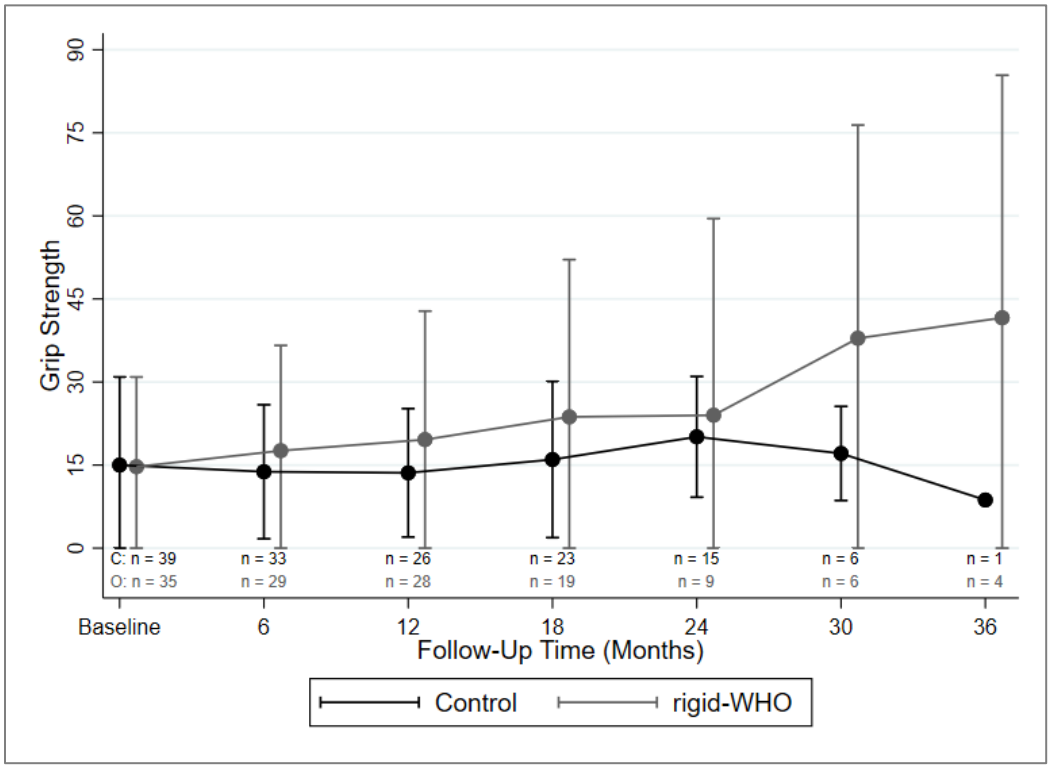

Figure 2. Repeated measures of range of movement of the wrist and grip strength.

Note. Figure 2a: Passive wrist extension with fingers extended; Figure 2b. Passive wrist extension with fingers flexed; Figure 2c. Active wrist extension with fingers extended; Figure 2d. Grip strength.

Figure 2. Alt Text. Four graphs showing comparisons between rigid-WHO and control group over time. Graph 2a displays passive range of movement of wrist extension with fingers extended. Graph 2b displays passive range of movement of wrist extension with fingers flexed. Graph 2c displays active range of movement of wrist with fingers extended. Graph 2d displays grip strength. Each graph shows few differences between groups over time.

Descriptive statistics by treatment group at each time point of the MAS for wrist extension with fingers extended and fingers flexed are presented in Supplementary Table 7. Distributions of children across categories of the House Thumb in Palm and NHDC are similar between groups. Mean scores are similar for each group on the Participation and Environment Measure for Children and Youth. See Supplementary Tables 8, 9 and 10 respectively.

Discussion

We implemented a pragmatic assessor-blinded RCT that originally aimed to investigate the effectiveness of the provision of rigid-WHO, for children with CP aged 5-15 years, on wrist range of movement and muscle stiffness, pain, activity performance and participation. The trial stopped early due to insufficient recruitment and resources, and so it is not possible to report definitive findings. On average, participants were in the study for approximately 18 months, with only five participants reaching the intended 36-month data collection point. Although under-powered, our sample size and time to follow up represent the largest trial with the longest follow up of upper limb orthosis wearing in the CP population to date.

Key findings

After adjusting for age and baseline measures, hand deformity severity and BFMF, our analyses suggested there was some evidence of benefit of rigid-WHO on the primary outcome, wrist extension with fingers extended, at 6 and 12 months and grip strength at 12 months. Adjusted mean differences between groups at 6 (13.15°) and 12 months (20.94°) were larger than the 10° difference at 3-years on which our sample estimate was based, but both CI ranges include values less than 10°. Smaller differences between groups on the primary outcome were observed past 12 months, and benefit for any other outcome at any time point was not observed. By the 18 months follow-up, participant numbers had reduced to 59, ~30% of the fully powered study, so likely to be insufficient to detect a difference if one existed.

The findings of potential benefits of the rigid-WHO at 6- and 12-months following prescription, contrast with the previously reported systematic review evidence (9) about the effect of stretch interventions. The systematic review found a pooled mean difference of only 2° (95%CI: 0° to 3°) (9). Differences may be explained by the short-term follow-up (≤7 months), and/or the diverse populations included (all ages, any neurological condition, upper and lower limbs), in the review samples. While our findings suggest an effect may be gained with longer-term wearing and/or in children with CP, they are limited by our inability to meet the study aims because of insufficient recruitment: cautious application of findings is recommended.

Our selection of the primary outcome (passive wrist extension with fingers extended) was based on the need to identify whether the rigid-WHO produced the intended effect of maintaining or increasing range of movement (by mobilising soft tissue) over time. Secondary outcomes were selected to identify any downstream impacts, should the mechanism of effect be demonstrated. Although some effect was observed on passive range of movement, our study showed little effect

of wearing a rigid-WHO on secondary outcomes. These findings are also limited by the trial being underpowered and stopping early.

Limitations

Despite careful preparation, funding of dedicated study staff, engagement with multiple trial sites and therapists, and robust implementation protocols, this trial could not be conducted as planned. The trial was initially funded with adequate resources for 5 years, however, with low recruitment trajectories, the cost of staff per recruited participant became unsustainable and the trial was stopped early. We recruited only 38% of our target of 194. Consistent with other trials (31), our actual capacity to recruit was much less than anticipated (11): we converted just 19.3% from 'interested to discuss the trial' to 'consented'. This is much less than the 70% reported by Realpe et al. (32) when developing their six-step model for recruitment. In our study, approximately 8% (n=30) of those with whom the trial was discussed, declined because their child was currently prescribed an orthosis and they did not wish to risk being allocated to the control group. A similar number (n=29) declined because they did not want to be allocated to the rigid-WHO group because of past experiences wearing one, or a belief it would not help. In addition to parent/caregivers, and on occasion the child or adolescent, declining for orthosis-specific reasons, it is likely there are others who were not referred to the study, or discouraged from participation by their treating therapists because they thought it wrong to cease wearing a rigid-WHO or they would not consider prescribing one.

Another limitation was the difficulties experienced in reliable recording of the rigid-WHO wearing schedule. TherApp was designed in 2013 to collect 'real-time' data on daily orthosis wear, and adverse events and concomitant therapy on a weekly basis. Technical difficulties associated with frequent operating system updates meant that parents/caregivers were unable to

provide data consistently and our measure of 'how much the rigid-WHO was worn', was compromised. Data that are available, confirm our clinical experiences of highly variable wearing times between participants, from never to routinely, but suggest that, on average, the rigid-WHO was worn about a quarter of the time. Importantly, when the orthosis was worn, it appeared possible to achieve the desired ≥6-hour wearing time.

Although TherApp data were not consistent, we supplemented information about additional interventions that focused on the upper limb through our 6-monthly study-specific questionnaire. These data suggest the groups were similar at baseline, however interpretation of changes over time are difficult given the declining sample sizes at each time point and difficulties quantifying the nature and intensity of varied interventions. Further evaluation of health service use, and cost-benefits of the rigid-WHO are reported elsewhere (12).

Although we established reliable measurement of our primary outcomes during assessor-training, goniometric measures without torque control is a limitation. At study inception existing torque control measures (33) were not reliably adaptable to small hands. Resolving this measurement problem is crucial for future research.

Clinical implications

Our original goal was to provide quality evidence for clinicians – either that rigid-WHO do not benefit children with CP, and the practice should cease, or that they do benefit, at least some children with CP. Unfortunately, we are unable to make clear recommendations. Our evidence suggests there may be incremental benefit at 6 and 12 months, for some children, on passive range of wrist extension measured with fingers extended with application of the rigid-WHO fabricated according to the principles used in this study. The reducing sample size beyond 18

months makes further recommendations impossible. Longitudinal follow up of children who are prescribed a rigid-WHO is needed to monitor any benefit. Important to note, is that our rigid-WHO positioning principles and associated protocol (Imms et al. 2016) which guided orthoses to support the musculotendinous unit in a lengthened position, were developed using expert consensus, and differ from past recommendations that the wrist and hand be placed in the resting position.

Our findings suggest that it may not be too late to provide rigid-WHO to children over the age of 5 years: our participants' mean age at baseline was 10 years (range 5.1 to 15.0 years). Rigid-WHO may, however, be more effective in younger children who do not yet have loss of passive wrist extension; and this requires further study. Our team has a trial in progress involving younger children (aged <3years at recruitment) which has reached its sample estimate target (Australia and New Zealand Clinical Trials Registry: U1111-1164-0647).

Our study also demonstrated that minor adverse events associated with the provision of a rigid-WHO were common, including sleep disturbance and localised skin or soft tissue irritation. We did not collect sleep disturbance data from our control group participants; therefore, it is not possible to identify the extent to which sleep problems differed between the groups, and sleep disturbance is frequent in children with CP (34). Although common, all minor events were of short duration – typically of only 1-2 weeks. Information regarding the frequency of minor adverse events should form part of the communication to children and families, and monitored, if clinicians are considering provision of rigid-WHO.

Research implications

We aimed to recruit enough participants to identify a small effect over a 3-year period on the assumptions that: (i) loss of ROM occurs incrementally; and (ii) that knowledge of long-term effects of this intervention for growing children was essential to inform clinical practice. Ultimately this was a costly and complex trial to implement, and we did not achieve our aims. Several qualitative studies have explored what it takes to recruit effectively into RCTs. While our protocols addressed many of the recommendations from those studies, we would emphasise the need for carefully adhering to them (35, 36).

Despite systematic review evidence indicating that passive stretch to soft tissues is not an effective method for maintaining or increasing range of movement (9), the findings of this study, although inconclusive, suggest a need for more information about whether children with CP may benefit over time. Like many interventions, this suggests a tailored, individualised approach to clinical decision-making is warranted.

Conclusion

The results of our study provide some evidence to support the use of rigid-WHO to change or prevent further loss of passive range of motion, at the wrist, for children aged 5-15 years with CP over a 12-month period. Little can be determined about the effect this intervention has on children's lives from activity performance, participation and quality of life perspectives given the smaller than anticipated participant numbers and early study cessation. Until a more definitive answer is found, the question remains as to whether the small benefit on passive range of motion is enough to support the prescription of rigid-WHO in the management of upper limb impairment in children with CP.

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Declaration in interests

The authors declare there are no competing interests to declare.

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