



Randomized Comparison Trial of Rehabilitation Very Early for Infants with Congenital Hemiplegia

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Objective To compare efficacy of constraint-induced movement therapy (Baby-CIMT) with bimanual therapy (Baby-BIM) in infants at high risk of unilateral cerebral palsy.

Study design This was a single-blind, randomized-comparison-trial that had the following inclusion criteria: (1) asymmetric brain lesion (2) absent fidgety General Movements, (3) Hammersmith Infant Neurological Examination below cerebral palsy cut-points, (4) entry at 3-9 months of corrected age, and (5) >3-point difference between hands on Hand Assessment Infants (HAI). Infants were randomized to Baby-CIMT or Baby-BIM, which comprised 6-9 months of home-based intervention. Daily dose varied from 20 to 40 minutes according to age (total 70-89.2 hours). Primary outcome measure was the HAI after intervention, with secondary outcomes Mini-Assisting Hand Assessment and Bayley III cognition at 24 months of corrected age.

Results In total, 96 infants (51 male, 52 right hemiplegia) born median at 37-weeks of gestation were randomized to Baby-CIMT (n = 46) or Baby-BIM (n = 50) and commenced intervention at a mean 6.5 (SD 1.6) months corrected age. There were no between group differences immediately after intervention on HAI (mean difference [MD] 0.98 HAI units, 95% CI 0.94-2.91; $P = .31$). Both groups demonstrated significant clinically important improvements from baseline to after intervention (Baby-BIM MD 3.48, 95% CI 2.09-4.87; Baby-CIMT MD 4.42, 95% CI 3.07-5.77). At 24 months, 64 infants were diagnosed with unilateral cerebral palsy (35 Baby-CIMT, 29 Baby-BIM). Infants who entered the study between 3 and 6 months of corrected age had greater change in HAI Both Hands Sum Score compared with those who entered at ≥ 6 months of corrected age (MD 7.17, 95% CI 2.93-11.41, $P = .001$).

Conclusions Baby-CIMT was not superior to Baby-BIM, and both interventions improved hand development. Infants commencing intervention at <6 months corrected age had greater improvements in hand function. (*J Pediatr* 2025;277:114381).

Congenital hemiplegia is present in 50% of children with cerebral palsy (CP), which is the most common physical disability in childhood.¹ Currently, 2 intensive upper-limb (UL) therapy approaches have high-quality evidence of efficacy in school-aged children with CP.² A bimanual approach (BIM) improves use of the impaired hand as an assisting hand in daily activities.³ Modified constraint-induced movement therapy (mCIMT) constrains the unimpaired hand in a glove to encourage intensive training of the hemiplegic arm.⁴ Our meta-analysis of interventions to improve UL function

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AHA	Assisting Hand Assessment	EASR	Emotional Availability-Self Report
Baby BIM	Child-friendly version of bimanual training	GMA	General Movements
Baby CIMT	Child-friendly version of constraint-induced movement therapy	HAI	Hand Assessment of Infants
BIM	Bimanual training	HINE	Hammersmith Infant Neurological Examination
BoHS	Both hands sum score	mCIMT	Modified constraint-induced movement therapy
BSID-III	Bayley Scales of Infant/Toddler Development, Third Edition	MD	Mean difference
CP	Cerebral palsy	RCT	Randomized controlled trial
DASS-21	Depression Anxiety Stress Scale	SDD	Smallest detectable difference
EaHS	Each Hand Sum Score	UCP	Unilateral cerebral palsy
		UL	Upper limb

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for school-age children with hemiplegia² found strong evidence that CIMT or mCIMT was more effective than usual care to improve UL function. Equal doses of mCIMT or bimanual therapy led to equal improvements in hand function.⁵ To date, these approaches have not been compared in a randomized controlled trial (RCT) in infants with asymmetric brain lesions commenced before 6 months of corrected age.⁴

Despite the need for early interventions to optimize neuroplasticity, there are limited phase 2 trials in infants younger than 12 months of corrected age.^{6,7} A pilot RCT of 27 infants with unilateral cerebral palsy (UCP) commenced at 3-8 months of corrected age found mCIMT compared with massage had significantly greater improvement on the Hand Assessment for Infants (HAI).⁶ There were no detrimental effects on the less-impaired hand, supporting safety and feasibility.^{8,9,10} A single-blind RCT of 33 infants with UCP (mean age 11.1 months of corrected age at entry) directly compared mCIMT with BIM.¹¹ Both groups demonstrated similarly large improvements on the Mini-Assisting Hand Assessment (AHA) posttreatment. We now test the efficacy of these 2 UL approaches commencing at <6 months corrected age. There has been speculation that BIM may benefit later bimanual coordination, whereas mCIMT may achieve earlier capability in the hemiplegic hand as the result of specificity of training. Other conclusions have been drawn from studies in animals in which the authors hypothesized that early mCIMT may have a deleterious effect on brain reorganization (overlateralization of corticospinal pathways), whereas equal training of both hands may reduce such an effect.¹² To date, however, neither of these approaches have been tested or compared in a definitive RCT in very young infants with asymmetric brain lesions.

As the first 2 years is the maximum period of brain reorganization of the CS motor projections¹³ and thalamocortical sensory projections, we proposed it could be useful to track development using advanced magnetic resonance imaging (MRI) techniques of the brain. Our previous work highlighted that the developing connectivity and symmetry of the thalamocortical pathways connecting M1 with the motor thalamus is as important as the symmetry of the CS tracts for unimanual capacity and bimanual coordination.¹² We found that microstructural measures of the sensorimotor thalamic tracts were more significantly correlated with paretic hand function than those of the CS tracts.¹⁴ These data suggest functional outcome is not only related to the integrity of the CS tract but also requires feedback from sensory systems to shape the motor cortex and underlying pathways. These data also suggest that equal bimanual training may be important not only for the developing contralateral corticospinal pathways but also for feedback from the ipsilateral thalamocortical tracts.

The present REACH (Rehabilitation EArly for Congenital Hemiplegia) study¹⁵ directly compared an infant-friendly mCIMT, called "Baby-CIMT," with an equally intensive bimanual approach, called "Baby-BIM" in very young infants with signs of UCP. The primary aim was to determine whether Baby-CIMT was more effective than Baby-BIM in

improving hand function on the HAI post intervention (at 12-15 months of corrected age). The secondary aims were (1) to test the differential effect of each approach on the ability to use the hemiplegic hand in bimanual play activities and cognitive development at 12-15 months of corrected age and 24 months corrected age; (2) to test the impact of early commencement (at 3-6 months of corrected age) compared with later commencement (>6 months of corrected age) on the HAI; (3) to test the impact on parent-child interaction, mental health, and social outcome measures according to treatment group allocation; and a final exploratory aim (4) was to test the differential effects each training approach on brain reorganization using advanced brain imaging at 2 years of corrected age. We hypothesized that a unimanual lateralized approach (Baby CIMT) would be more effective than an equal bimanual approach at improving early hand function as measured on the HAI.

Methods

The REACH study was conducted in Australia and the US between January 2015 and December 2022. Parents provided informed consent for their child's participation. The trial is reported according to CONSORT guidelines.¹⁶ The study protocol was published a priori according to the SPIRIT protocol.¹⁵ Full ethical approvals were obtained from all study sites (see the Acknowledgments).

Study Sample

Infants were screened for high risk of UCP according to the Clinical Practice Guideline.¹⁷ Participants were recruited at 3-9 months of corrected age. Variation to the original protocol extended the recruitment age from ≤6 months to ≤9 months because of slow recruitment rates. Infants were included with the following criteria:

1. Unilateral or asymmetric brain lesion on cranial ultrasound or MRI; and
- 2a Absent fidgety movements on General Movements Assessment (GMA) or
- 2b Low Hammersmith Infant Neurological Examination (HINE) below the CP cut-points^{10,18-20} (HINE at 3 months <57, at 6 months <60, at 9 months <63); and
3. UL asymmetry (>3-point difference on HAI between limbs congruent with neuroimaging).

Exclusion criteria were as follows:

1. Epilepsy uncontrolled by medication;
2. Retinopathy of prematurity greater than grade 2 or cortical blindness or limited visual tracking as it was likely to influence their ability to participate in the intervention (ie, reaching, grasping toys in visual range);
3. Presence of ventriculoperitoneal shunt, as such was likely to be a confound to development as reorganization after the brain lesion may not be stable after surgery so that brain reorganization may not be due to the type of therapy but rather the recovery after shunt surgery.

Study Design and Data Collection

This single-blind RCT compared equal doses of Baby-CIMT and Baby-BIM in infants at high risk of UCP. Central randomization was concealed using an electronic allocation system, stratified by age at entry (3 to 5 months or 6 to 9 months of corrected age), sex, and side of brain lesion (right/left). The treating therapist was notified by the central coordinator after completion of baseline assessments.

Assessments

Outcomes were measured at baseline (T0, at 3-9 months of corrected age), at 6 months on the HAI, immediately postintervention at 12-15 months of corrected age depending on age at study entry (T1) and at 24 months of corrected age (T2). Because of the protocol variation in age eligibility requirements, not all infants received a 6-month assessment. The 6-month assessment time point was used in the analysis if it was the baseline measure for the infant. At baseline, socioeconomic status, parental education, birth history, and comorbidities were surveyed.

Primary Outcome (T1). The HAI^{2,5,21} is an observation-based test that is scored 0-100 for infants 3-12 months that evaluates quality and frequency of hand use.²² The HAI is criterion norm referenced with Rasch construct validity. The smallest detectable difference (SDD) is 2 points for the Each Hand Sum Score (EaHS) and 3 HAI units for bimanual hand performance.²³ Only 1.8% of healthy children have a difference of 3-5 points between hands,²⁴ so a difference of >3 points was likely to indicate asymmetric hand function and risk of UCP.²³ The HAI was scored by an accredited rater masked to group allocation. The original study protocol¹⁵ had the AHA as the primary outcome however this was changed to the HAI as the primary outcome after it was published as it is more suitable for the age range 3-16 months of corrected age.

Secondary Outcomes. Use of the hemiplegic hand in bimanual activities was assessed using the Rasch-developed Mini-AHA (T1) and Small Kids AHA (T2).^{22,25} The Small Kids AHA has a SDD of 3.89 raw scores.⁴ The Mini-AHA is valid and reliable.²⁶ Bayley Scales of Infant/Toddler Development, Third Edition (BSID-III)²⁷ (cognitive and motor domains) have good test-retest reliability 0.67 (fine motor) and 0.83 (gross motor).²⁵ Pediatric Evaluation of Disability Inventory Computer Adapted Test is a norm referenced, parent-reported performance measure of daily activities, mobility and social functioning with good validity and reliability.²⁸ Emotional Availability-Self Report (EA-SR)²⁹ is a parent self-report measure of emotional availability with excellent reliability and validity. Depression Anxiety Stress Scale (DASS-21)³⁰ assesses depression, anxiety, and stress in the mother.³⁰ The Social Risk Index is a composite score of social status across 6 items (0-3 per item)³¹ where <3 indicates greater risk.³² The Pediatric Rehabilitation Intervention Measure of Engagement-General³³ is parent-reported engagement.³⁴ Clinical neuroimaging of the brain

undertaken in the newborn period was retrieved at recruitment to classify the type and brain lesion severity, laterality, and asymmetry of the brain lesion. Follow-up MRIs at 3T were offered at 3 of the 5 recruiting sites as either sleeping scans or under sedation.

Study Interventions

For more details, the reader is referred to the published protocol.¹⁵

Common to Both Approaches. Parents carried out one of the interventions randomly allocated at home using a therapist guided written program.³⁵ Bimonthly home visits were provided by a trained pediatric therapist, in addition to bimonthly virtual remote sessions. Four ability levels of the therapy program were determined to provide each child with a “just-right” challenge and to increment the challenge: (1) pre-grasp and reaching, (2) achieving grasp, (3) further grasping and object manipulation, and (4) refinement of grasping and object manipulation.²¹ Selection of the ability level was guided by HAI scores.^{36,37} Both interventions supported parents’ mental health and responsive parenting based on emotional availability^{35,38} and Acceptance and Commitment Therapy.³⁹

Parents provided therapy in 1-3 sessions per day, 5 days/week for a total of 6-9 months, according to age at study entry. The daily dose varied with age, with total dose 70-89.2 hours depending on entry age. Parents completed a daily diary of home-based practice, which was reviewed by the therapist at each home visit and uploaded on a central database (REDCap). The home practice diary recorded the amount of daily home practice (in minutes), the activities practiced and any questions for the therapist at the subsequent contact. During the home sessions, the infant was seated in an upright infant chair with a tray to allow goal directed arm use and focus on the task.⁴⁰

- i. Baby-CIMT¹⁰ comprised restriction of the less-impaired limb using a soft restraint (eg, glove, not a rigid cast) combined with intensive play-based training of the hemiplegic arm. Carefully selected age-appropriate engaging toys provoked self-generated movements of the hemiplegic hand⁴¹ as developed with Eliasson et al.^{6,9,42}
- ii. Baby-BIM comprised play-based activity encouraging use of both the hemiplegic and less impaired ULs together during bimanual activities⁴³ as developed by Greaves et al.^{36,41} Engaging, age appropriate toys, and tasks required 2 hands with environmental adaptation were used to provoke bimanual training.⁴⁴

To ensure fidelity all therapists undertook training in HAI (3 days), Mini-AHA (3 days), and intervention delivery (2 days on each approach). This initial training was followed by regular monthly community of practice sessions where therapists presented cases for discussion and feedback. Both interventions were protocolized and confidentially maintained within study personnel to avoid contamination.

Home visits were videorecorded. The first 2 and 10% of further home visits were reviewed independently to confirm study fidelity against a Treatment Fidelity Checklist.⁴⁵ Therapists were trained on both interventions, and a fidelity protocol was put in place to avoid contamination of one therapy into the other approach. Concomitant interventions (eg, physical therapy, occupational therapy) during the study period and up until 24 months of corrected age were recorded. Adverse events were screened at 6, 12, and 24 months of corrected age by non treating personnel. Families were monitored for parent mental health using the DASS-21³⁰ and EA-SR.²⁹

Confirmation of Diagnosis/Motor Distribution. At 12 and 24 months of corrected age, diagnosis of UCP and comorbidities were confirmed by a physician. Motor type was classified according to SCPE guidelines,⁴⁶ and HINE was performed at 12 and 24 months of corrected age.^{10,18-20} Where available, MRI of the brain was used to assess asymmetry of unilateral/bilateral brain lesions using a semi-quantitative scale.⁴⁷

Sample Size

Our original sample size was based on 2- to 3-year-old patients⁹ with a difference of 6 AHA logit points (0-100 Scale)^{48,49} with an SD of 12.8 units⁵ as the minimum difference to have clinical impact. A 6-unit difference on AHA with 80% power required a sample size of 144 participants (72 per group, 2-sided $\alpha = 0.05$) so a sample of 150 children (75 in each group) was proposed. After the study protocol was published, the order of the Mini-AHA and HAI outcomes was reversed, and HAI was defined as the primary outcome as it is a valid and reliable measure of hand development across the intervention period from 3 to 15 months of corrected age. With 144 participants, and assuming SD = 6.0, then we had 80% power to find a clinically important between-group difference of at least 2.8 HAI impaired EaHS units.

Statistical Analysis

HAI scores postintervention were compared between treatment groups using a generalized linear model with a Gaussian family and identity link function, with study group included as the fixed effect and baseline HAI as a covariable. Secondary outcomes used similar models. Effect estimates of mean difference (MD) and 95% CI were calculated for all primary and secondary data with continuous outcomes. Assumptions of regression were checked. HAI scores postintervention were compared between treatment groups using a generalized linear model with a Gaussian family and identity link function, with study group included as the fixed effect and baseline HAI as a covariable. This is equivalent to a linear regression model adjusting for baseline values. Secondary outcomes used similar models.

One outlier was removed for all HAI, Mini-AHA, and AHA analyses. Analyses were completed on the full data

set, and then for the subset of participants diagnosed with UCP by study completion. Analyses were intention-to-treat, with significance $P < .05$. An analysis investigating the association between age at enrollment (3^{6/7} to 9 months) and outcomes was undertaken using generalized linear models. Age-adjusted Z scores for baseline EaHS for the impaired hand and both hands sum score (BoHS) were calculated based on normative values.⁵⁰ When investigating the association by age, these variables were used as covariables to account for different ages and ability levels at baseline (version 17, StataCorp).

Results

Ninety-six infants at high risk of UCP were recruited and randomized to Baby-CIMT ($n = 46$) or Baby-BIM ($n = 50$) (**Figure 1**). Study groups were balanced for demographic and clinical characteristics (**Table I**). There were more male infants (52%) and more right-sided UCP ($n = 52$ [54%]) with unilateral (60 [69%]) or asymmetric bilateral brain lesions (27 [31%]), consistent with CP populations.⁵¹ The mean age at entry was 5.5 months of corrected age and 13 months of corrected age post intervention. The mean age post intervention for the early-entry group (entered between 3 and 6 months of corrected age) was 12.2 months (SD 0.67) and late group (entered >6 months of corrected age) was 14.5 months (SD 1.08). To meet entry criteria, children had either absent fidgety GMA (49%), HINE below cut-points for age (76%), HINE >5 asymmetries (24%), and all had > 3-point difference between hands on the HAI (100%) and/or MRI findings for uni-asymmetric brain injury (**Table I**). All HAI asymmetries were congruent with the brain lesions on MRI or cranial ultrasound. Interventions occurred at 5 sites with equivalent distribution by group. At completion, there was 42 infants (84%) in Baby-BIM and 43 infants (93%) in Baby-CIMT. Eleven participants were lost to follow-up (12%), and there was no difference with those who completed follow-up. Reasons for attrition are detailed in **Figure 1**. No adverse events were reported in either group. The dose of direct intervention delivered by parents or therapists was similar between groups (**Table I**). There was, however, wide variability in home practice for Baby-CIMT (mean 43.2, SD 21.3 hours) and Baby-BIM (mean 46.0, SD 23.9 hours). Therapist delivery ($n = 64$, 88.9%) of both interventions demonstrated high fidelity on the Treatment Fidelity Checklist ($\geq 13/16$).⁴⁵ Parents reported equally high engagement with both approaches on the Pediatric Rehabilitation Intervention Measure of Engagement-General.³⁴

Primary Outcome

There were no differences between groups on overall HAI units immediately post intervention (MD 0.84, 95% CI -4.03 to 5.70; $P = .77$) (**Table II**). Both groups demonstrated

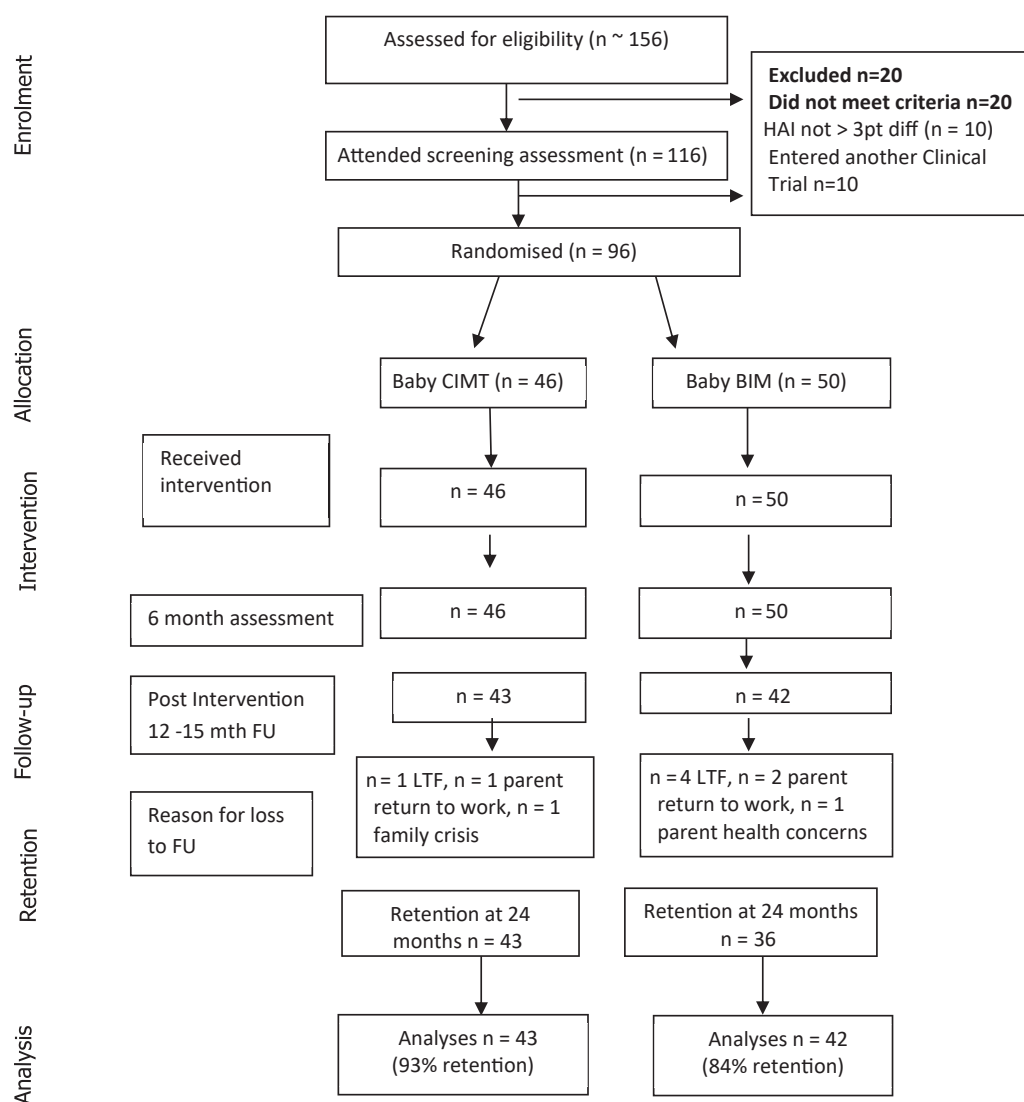


Figure 1. Trial profile following CONSORT guidelines. *FU*, follow-up; *LTF*, lost to follow-up.

significant improvements from T0 to T1 (Baby-BIM MD 13.7 HAI units, 95%CI 10.2, 17.6, $P < .001$; Baby-CIMT MD 15.9 units, 95%CI 11.7, 20.1, $P < .001$). There were no significant differences between groups on HAI impaired EaHS at T1 (Table II, Figure 2). From T0 to T1, both groups demonstrated significant improvements in HAI-impaired EaHS (Baby-CIMT: MD 4.42, 95% CI 3.07-5.77, $P < .001$; Baby-BIM: MD 3.48, 95% CI 2.09-4.87, $P < .001$). Both groups also had a significant increase in scores on the less impaired hand.

Secondary Outcomes

There were no significant differences between groups on the Mini-AHA at T1 (MD 5.4, 95% CI -5.83 to 16.68; $P = .34$) or AHA at T2 (MD -5.34, 95% CI -5.39 to 16.06; $P = .33$) (Table II). There were no significant between-group differences on BSID-III cognitive or motor domains,

Pediatric Evaluation of Disability Inventory Computer Adapted Test Daily Activities, Mobility, or Social Communication Domains at T1, T2 except BSID-III Gross Motor Domain favoring the Baby-BIM group at T2 (Table II). Sensitivity analyses post-hoc on the subgroup of 64 infants with a confirmed diagnosis of UCP (Table II) were 35 (81%) participants in Baby-CIMT and 29 (69%) in Baby-BIM. At 24 months of corrected age, there was a greater number of children diagnosed as having asymmetric bilateral CP in the Baby-BIM ($n = 6.14\%$) compared with the Baby-CIMT group ($n = 2.4\%$). Both groups had an equal number of children who did not have a diagnosis or any clinical signs of CP ($n = 7.16\%$).

Infants who entered the study earlier between 3 and 6 months of corrected age had significantly greater change in BoHS (MD 7.17, 95% CI 2.93-11.41; $P = .001$) and HAI-impaired EaHS (MD 4.77, 95% CI 1.68-7.86; $P = .002$)

Table I. Baseline characteristics of the sample by group

Characteristics	Total (n = 96)	Intervention group		P value
		Baby-CIMT (n = 46)	Baby-BIM (n = 50)	
Sex				
Male, No. (%)	51 (53%)	24 (52%)	27 (54%)	.86
Female, No. (%)	45 (47%)	22 (48%)	23 (46%)	
Gestational age at birth, wk				
Median (IQR)	37 (30.2-39.2)	35.6 (30,39.5)	37.5 (34.2, 39.2)	.18
Method of delivery, No. (%)				.56
Vaginal	34 (35%)	14 (30%)	20 (40%)	
Forceps	1 (1%)	0	1 (2%)	
Vacuum	2 (2%)	1 (2%)	1 (2%)	
Cesarean	59 (62%)	31 (68%)	28 (56%)	
Birth weight, kg, median (IQR)	2.87 (1.46-3.51)	2.31 (1.46-3.51)	3.13 (1.66-3.5)	.47
Age at intervention start, mo				
Mean (SD)	6.45 (1.58)	6.56 (1.63)	6.35 (1.54)	.59
Laterality of impairment, No. (%)				
Right	52 (54%)	25 (54%)	27 (54%)	1.00
Left	44 (46%)	21 (46%)	23 (46%)	
Hemisphere side				
Right, No. (%)	52 (54%)	25 (54%)	27 (54%)	1.00
Left, No. (%)	44 (46%)	21 (46%)	23 (46%)	
Laterality of brain lesion				
Unilateral, No. (%)	60 (69%)	28 (67%)	32 (71%)	.65
Asymmetric bilateral, No. (%)	27 (31%)	14 (33%)	13 (29%)	
Eligibility criteria, n				
GMA (absent F/abnormal F)	47/2 (49%/2%)	21/1/(45%/2%)	26/1 (52%/2%)	
HINE (below CP cut-point)	13/17 (76%)	4/7 (0.08%/1.5%)	9/10 (18%/20%)	
HINE asymmetric (>5), No. (%)	23 (24%)	10 (22%)	13 (26%)	
HAI >3-point diff	96/96 (100%)	46/46 (100%)	50/50 (100%)	
MRI of the brain, No.				
PVL/IVH	5/9	3/6	2/3	
Corrected age/other	8/5	3/3	5/2	
Parietal-occipital/frontal	3/3	2/1	1/2	
No MRI report		18 (54%)	19 (56%)	
Comorbidities				
Epilepsy	13 (14%)	8 (17%)	5 (10%)	.29
Retinopathy of prematurity	12 (13%)	5 (11%)	7 (14%)	.64
Hydrocephalus	6 (6%)	3 (6%)	3 (6%)	.92
Corrected age at baseline				
mo, mean (SD)		5.4 (1.7)	5.9 (1.6)	.18
Corrected age at post Rx Ass				
mo, mean (SD)		12.7 (1.2)	13 (1.4)	.26
Baseline HAI impaired EaHS				
Mean (SD)	10.31 (5.92)	11.1 (5.6)	9.1 (6.0)	.10
Early group (entered 3-6 mo), mo, mean (SD)	12.2 (0.67)			
Late-entry group (entered >6 mo), mo, mean (SD)	14.5 (1.08)			
Baseline unimpaired EaHS, mean (SD)		21.5 (3.6)	21.1 (2.6)	.55
Base HAI asymmetry, mean (SD)		49.3 (22.4)	57.9 (26.4)	.09
Base HAI units, mean (SD)		55.5 (13.6)	51.4 (11.0)	.10
Sample and Intervention by site				
New South Wales	12 (13%)	7 (15%)	5 (10%)	.33
Ohio	12 (13%)	5 (11%)	8 (16%)	
Queensland	34 (35%)	19 (41%)	15 (30%)	
Victoria	16 (17%)	9 (20%)	7 (14%)	
Western Australia	20 (21%)	6 (13%)	14 (28%)	
Minnesota	1 (1%)	0	1 (2%)	
Intervention delivery				
Number of Therapy Sessions, mean (IQR)	12 (10, 14)	12 (10, 13)	12 (10, 13)	
Home practice mean, h (IQR)	44.6 (22.6)	43.2 (21.3)	46.0 (23.9)	.60
Received concomitant therapy		45 (98%)	34 (68%)	
Therapist fidelity score, Median (IQR)	16 (14, 16)	16 (15, 16)	16 (14, 16)	
Parent engagement, Median (IQR)	82 (76, 84)	82 (77, 84)	82 (73, 83.5)	
Social Risk Index, median (IQR)	1 (0, 2)	1 (1, 2)	1 (0, 2)	.59
Lower social risk, No. (%)	71 (78.9%)	37 (80.4%)	34 (77.3%)	
Greater social risk, No. (%)	19 (21.1%)	9 (19.6%)	10 (22.7%)	

IVH, intraventricular hemorrhage; PRIME-G, Pediatric Rehabilitation Intervention Measure of Engagement-General; PVL, periventricular leukomalacia.

P values of Fisher exact tests were used for categorical variables and Mann-Whitney U tests for ordinal and continuous variables. For social risk index, lower social risk score from 0 to 2, and greater social risk is 3 or greater.

Table II. Association between group allocation and primary and secondary outcomes

Variables	Baseline, mean (SD)	12-15 mo, mean (SD)	24 mo, mean (SD)	12-15 mo between group difference	24 mo between group difference	BL to 12-15 mo within group difference	BL to 24 mo within group difference
HAI units							
Baby-CIMT	55.5 (13.6)	70.7 (16.7)	NA	0.84 (−4.03, 5.70) $P = .77$	NA	15.86 (11.66, 20.06) $P < .001$	NA
Baby-BIM	51.4 (11.0)	66.3 (17.6)	NA			13.86 (10.16, 17.56) $P < .001$	
HAI Imp EaHS							
Baby-CIMT	11.1 (5.6)	15.2 (6.7)	NA	0.54 (−1.24, 2.32) $P = .55$	NA	4.42 (3.07, 5.77) $P < .001$	NA
Baby-BIM	9.1 (6.0)	13.4 (7.5)	NA			3.48 (2.09, 4.87) $P < .001$	
HAI Unimp EaHS							
Baby-CIMT	21.5 (3.6)	21 (2.7)	NA	−0.08 (−0.40, 0.25) $P = .64$	NA	2.26 (1.12, 3.39) $P < .001$	NA
Baby-BIM	23.8 (0.9)	23.8 (0.6)	NA			2.67 (1.81, 3.52) $P < .001$	
HAI Asymm							
Baby-CIMT	49.3 (22.4)	57.9 (26.4)	NA	−4.06 (−11.96, 3.84) $P = .31$	NA	−14.30 (−19.55, −9.05) $P < .001$	NA
Baby-BIM	36.2 (27.8)	44.6 (31.8)	NA			−10.45 (−16.44, −4.47) $P = .001$	
Mini-AHA							
Baby-CIMT	NA	62.9 (25.4)	NA	5.4 (−5.83, 16.68) $P = .34$	NA	NA	NA
Baby-BIM	NA	55.7 (27.7)*	NA				
AHA							
Baby-CIMT	NA	NA	64.1 (21.3)	NA	5.34 (−5.39, 16.06) $P = .33$	NA	NA
Baby-BIM	NA	NA	58.8 (26.9) [†]				
PEDI-corrected ageT DA							
Baby-CIMT	NA	43.4 (2.9) [‡]	48.2 (3.8) [‡]	−0.63 (−1.94, 0.68) $P = .34$	0.14 (−1.38, 1.66) $P = .85$	NA	NA
Baby-BIM	NA	42.8 (3.2) [§]	48.4 (2.9) [¶]				
PEDI-corrected ageT Mob							
Baby-CIMT	NA	50.8 (3.8) [‡]	50.6 (3.4) [‡]	−0.2 (−1.75, 1.35) $P = .80$	0.93 (−0.86, 2.72) $P = .31$	NA	NA
Baby-BIM	NA	50.6 (3.4) [§]	58.5 (3.4) [¶]				
PEDI-corrected ageT Social							
Baby-CIMT	NA	50.7 (3.1) [‡]	50.7 (2.9) [‡]	0.05 (−1.24, 1.34) $P = .93$	0.52 (−1.25, 2.29) $P = .56$	NA	NA
Baby-BIM	NA	56.1 (2.8) [§]	55.6 (5) [¶]				
BSITD-III Cog							
Baby-CIMT	NA	95.9 (14.2)	87.2 (11.6)	3.14 (−2.98, 9.26) $P = .31$	0.09 (−5.37, 5.55) $P = .97$	NA	NA
Baby-BIM	NA	92.7 (13.4)	87.1 (12.6)**				
BSITD-III Motor							
Baby-CIMT	NA	82.6 (15.9)	82.7 (13.6)	−0.35 (−7.12, 6.42) $P = .92$	−0.41 (−6.75, 5.93) $P = 0.90$	NA	NA
Baby-BIM	NA	82.9 (14.7)	83.1 (14.4)**				
BSITD-III GM							
Baby-CIMT	NA	5.4 (3.8)	5.7 (2.9)	−0.12 (−1.64, 1.40) $P = .88$	−1.03 (−2.47, 0.41) $P = .16$	NA	NA
Baby-BIM	NA	5.5 (3.0)	6.7 (3.5)**				
BSITD-III FM							
Baby-CIMT	NA	9 (3)	8.82 (2.7)	0.28 (−1.01, 1.57) $P = .67$	−0.04 (−1.37, 1.29) $P = .95$	NA	NA
Baby-BIM	NA	8.9 (2.8)	8.9 (3.2)**				
DASS-21 ^{††} Depress							
Baby-CIMT	3 (3.5)	3.1 (5.9) [§]	3.5 (4.6)	−0.89 (−2.77, 1.0) $P = .35$	0 (−1.53, 1.53) $P = 1$	0.34 (−1.33, 2.02) $P = .68$	0.5 (−0.58, 1.63) $P = .34$
Baby-BIM	4.8 (6.2)	3.2 (3.8) ^{‡‡}	2.5 (3.8) ^{§§}			−0.05 (−1.25, 1.15) $P = .93$	−1.09 (−2.13, −0.06) $P = .04$
DASS-21 ^{††} Anxiety							
Baby-CIMT	2.4 (3.7) ^{¶¶}	2.3 (5.6) [§]	3.2 (5.0)	−0.22 (−2.40, 2.0) $P = .84$	0.33 (−0.39, 1.06) $P = .37$	0.2 (−1.34, 1.73) $P = .8$	0.95 (−0.33, 2.23) $P = .14$
Baby-BIM	3.3 (5)	2.4 (3.4) ^{‡‡}	2 (3.4) ^{§§}			0 (−1.09, 1.09) $P = 1$	−0.55 (−1.93, 0.84) $P = .43$

(continued)

Table II. Continued

Variables	Baseline, mean (SD)	12-15 mo, mean (SD)	24 mo, mean (SD)	12-15 mo between group difference	24 mo between group difference	BL to 12-15 mo within group difference	BL to 24 mo within group difference
DASS-21 ^{††} Stress							
Baby-CIMT	8 (5.8) ^{¶¶}	7.4 (7.5) [§]	8.2 (6.1)	0 (−3.42, 3.42) <i>P</i> = 1	1 (−1.12, 3.12) <i>P</i> = .35	−0.49 (−2.6, 1.62) <i>P</i> = .64	0.12 (−1.55, 1.79) <i>P</i> = .89
Baby-BIM	8.9 (7.4)	6.9 (5.6) ^{‡‡}	6.2 (5.3) ^{‡‡§§}			−0.68 (−2.93, 1.58) <i>P</i> = .55	−1.91 (−3.89, 0.74) <i>P</i> = .06
EA-SR Mutual							
Baby-CIMT	32.2 (4.3) ^{¶¶}	32.2 (4.7) [§]	31.0 (4.6)	1.53 (−0.27, 3.34) <i>P</i> = .095	0.04 (−2.11, 2.18) <i>P</i> = .97	0.56 (−0.91, 2.04) <i>P</i> = .45	−1.12 (−2.65, 0.41) <i>P</i> = .15
Baby-BIM	32.7 (4)	31.8 (4.9) ^{***}	31.4 (5.1) ^{§§}			−1.49 (−2.72, −0.26) <i>P</i> = .02	−1.82 (−3.7, 0.06) <i>P</i> = .06
EA-SR Child ^{††} Involvement							
Baby-CIMT	30.3 (4.7) ^{¶¶}	31.3 (5.2) [§]	33.2 (3.9)	1 (−1.70, 3.70) <i>P</i> = .46	1 (−1.04, 3.03) <i>P</i> = .33	0.9 (−1.02, 2.83) <i>P</i> = .35	2.86 (1.17, 4.54) <i>P</i> = .001
Baby-BIM	29.2 (4.2)	31.0 (4.7) ^{***}	32.5 (4.1) ^{§§}			1.46 (−0.02, 2.95) <i>P</i> = .053	3.33 (1.62, 5.05) <i>P</i> < .001
EA-SR Affect							
Baby-CIMT	19.0 (1.9) ^{¶¶}	18.5 (1.5) [§]	18 (1.8)	0.12 (−0.60, 0.84) <i>P</i> = .75	−0.85 (−1.60, −0.10) <i>P</i> = .03	−0.66 (−1.34, 0.02) <i>P</i> = .06	−1.19 (−1.9, −0.48) <i>P</i> = .002
Baby-BIM	18.6 (1.5)	18.3 (1.7) ^{***}	18.7 (1.3) ^{§§}			−0.37 (−1.02, 0.29) <i>P</i> = .27	
EA-SR Intrusive							
Baby-CIMT	14.5 (3.6) ^{¶¶}	13.81 (3.4) [§]	14 (3.8)	0.05 (−1.18, 1.29) <i>P</i> = .93	0.12 (−1.29, 1.53) <i>P</i> = .87	−0.71 (−1.65, 0.24) <i>P</i> = .14	−0.43 (−1.62, 0.76) <i>P</i> = .47
Baby-BIM	14.8 (3.2)	13.7 (3.0) ^{***}	13.9 (3) ^{§§}			−0.83 (−1.99, 0.33) <i>P</i> = .16	−0.55 (−1.78, 0.69) <i>P</i> = .38
EA-SR Hostility ^{††}							
Baby-CIMT	1.5 (2.3) ^{¶¶}	1.6 (2.7) [§]	3.5 (3.9) [×]	−1 (−2.15, 0.15) <i>P</i> = .09	−1.13 (−3.26, 1.01) <i>P</i> = .3	1.2 (−0.97, 1.02) <i>P</i> = .96	1.98 (0.71, 3.2) <i>P</i> = .003
Baby-BIM	1.6 (2.7)	2.6 (3.6) ^{***}	5 (4.5) ^{§§}			1.10 (0.46, 2.15) <i>P</i> = .04	3.24 (1.73, 4.75) <i>P</i> < .001

BL, baseline; Imp, impaired hand; NA, not available; *PEDI-corrected ageT*, Pediatric Evaluation of Disability Inventory Computer Adapted Test; *Unimp*, unimpaired hand.

Note at baseline *n* = 46 for Baby-CIMT and *n* = 50 for Baby-BIM, 12-15 month follow-up *n* = 43 for Baby-CIMT and *n* = 42 for Baby-BIM and at 24 months follow-up *n* = 44 for Baby-CIMT and *n* = 36 for Baby-BIM unless otherwise indicated.

**n* = 38.

†*n* = 36.

‡*n* = 43.

§*n* = 42.

¶*n* = 37.

***n* = 35.

††Values derived by quantile regression.

‡‡*n* = 40.

§§*n* = 33.

¶¶*n* = 44.

****n* = 41.

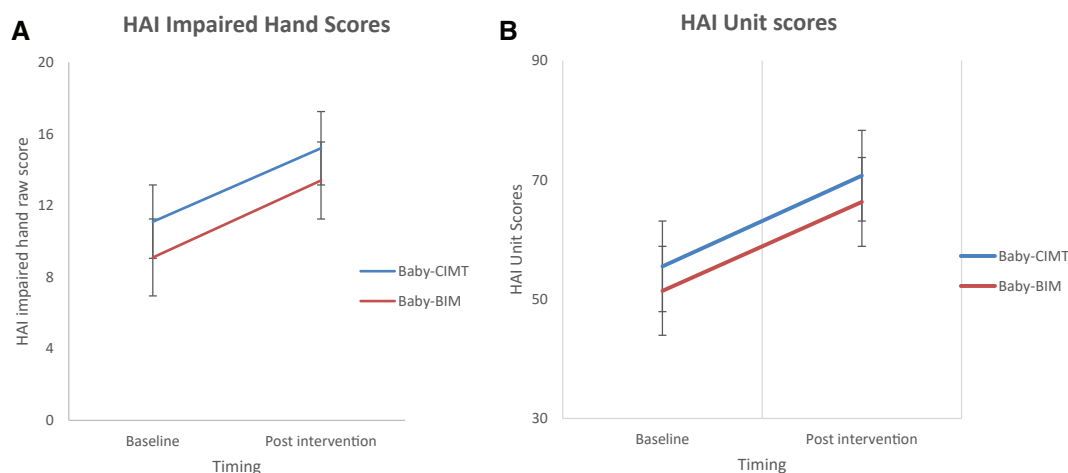


Figure 2. A and B, HAI between groups baseline to posttraining for the Baby CIMT group ($n = 43$) and Baby BIM group ($n = 42$). Between-groups analysis: CIMT vs BIM: MD 4.46, 95% CI -2.95 to 11.86; $P = .2$. Within-groups analysis over time: Baby CIMT: MD 13.86, 95% CI 10.16-17.56; $P < .001$, Baby BIM: MD 15.86, 95% CI 11.66-20.1; $P < .001$.

compared with those who entered after >6 months of corrected age, after adjusting for baseline BoHS and EaHS z scores (Figure 3).⁵⁰

Our data found that the DASS-21 and hostility scores for all parents in both groups were in the normal range at baseline. Study therapists received extensive training on promoting parent emotional availability and support of parents experiencing elevated stress and other mental health challenges from our study psychologist. There were occasions during which additional guidance was provided; however, none required referral for additional mental health support and therefore were not considered to be adverse events. Post intervention, the only significant difference between groups for parental mental health or emotional availability was for affect at T2 favoring Baby-BIM (MD -0.9, 95% CI -1.60 to -0.10, $P = .03$). Both groups showed improvements in child involvement on the EA-SR (Baby-CIMT MD 2.9, 95% CI 1.17-4.54, $P = .001$; Baby-BIM MD 3.3, 95% CI 1.62-5.05, $P < .001$) and increases in parent hostility (Baby-CIMT MD 2.0, 95% CI 0.71-3.2, $P = .003$; Baby-BIM MD

3.2, 95% CI 1.73-4.8, $P < .001$). The Baby-BIM group also showed significant decreases in parental depression (MD -1.1, 95% CI -2.13 to -0.06, $P = .04$).

Discussion

Baby-CIMT was not more effective than Baby-BIM as UL performance improved in both groups post intervention at 12-15 months of corrected age. These improvements on the HAI and Mini-AHA were maintained at 24 months of corrected age on the AHA. Both Baby-CIMT and Baby-BIM, are safe, feasible, and effective when commenced at 3-9 months of corrected age. At 24 months of corrected age, no differences were found between the Baby-CIMT and Baby-BIM groups for cognition, performance of daily activity, mobility, social function, gross-motor, and fine-motor function, reflecting the similar effect of 2 active interventions. In the subgroup of children with UCP, the Baby-BIM group had better BSID-III Gross Motor Scores at 24 months of corrected age potentially because of better stabilization of the

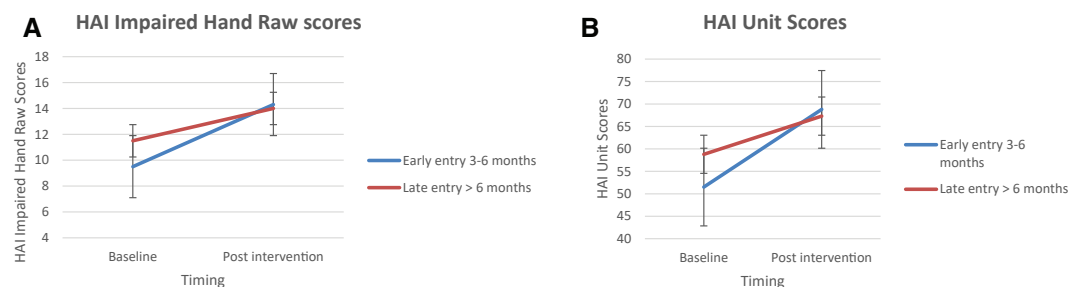


Figure 3. A and B, Hand Assessment of Infants scores for early (3-6 months of corrected age, $n = 67$) vs late entry (at 7-9 months of corrected age, $n = 29$). Early group on the HAI postintervention compared with the late entry group (HAI hemiplegic hand EaHS MD 4.8, 95% CI 1.7-7.9; $P = .002$). Infants who commenced Rx at 3-6 months had faster development compared with those who entered later at 6-9 months (HAI BoHS: early vs late: MD 7.2, 95% CI 3.97-17.69; $P = .002$).

hemiplegic hand during gross motor activities such as crawling.

Infants who commenced either UL intervention at 3-6 months of corrected age had a faster increase (~10 HAI units) in hand use on the HAI than infants who had later entry at 7-9 months of corrected age. This provides support for earlier commencement of intensive UL training to optimize outcomes thereby promoting neuroplasticity. These data need to be viewed in the context of normal developmental trajectories on the HAI,⁵⁰ which show that raw HAI scores typically increase from 3 to 6 months and then plateau after 6 months.⁵⁰ Children who began at 3-5 months also received an extra 2-3 therapy visits. The challenge for clinicians and researchers in commencing UL rehabilitation very early is the accurate identification of infants at risk of UCP using GMA, HINE, and MRI which in combination are 98% accurate for CP by 4 months.⁵²

Differences in EaHS on the HAI provide good discrimination and predictive validity for UCP between 6 and 15 months of corrected age²⁴ but were less apparent between 3 and 4 months of corrected age.⁵⁰ These differences may be attributable to the major use-dependent reorganization of CS projections by 6 months of corrected age. The first 3-6 months after an asymmetric brain lesion provide a critical opportunity for interventions to influence lateralization of the CS pathways.⁵⁰ When sparing of the CS tracts is present, early intervention may shape cortical reorganization and improve outcomes.⁵³ Our study confirmed that both the “one-handed” approach Baby-CIMT and “equal two-handed approach” Baby-BIM improved early hand development.

At 24 months of corrected age, there was a greater number of children with asymmetric bilateral CP in the Baby-BIM compared with the Baby-CIMT group, which may reflect the slightly greater mean HAI asymmetry score and lower mean HAI Units in the Baby-BIM group at study entry. It is uncertain how many children had asymmetric bilateral lesions compared with unilateral lesions at 24 months of corrected age, as a follow-up MRI under general anesthesia was not supported by clinicians and not accepted by parents. As the first 2 years is the maximum period of brain reorganization of the CS motor projections and thalamocortical sensory projections, it would be useful to track development using advanced MRI techniques for the brain.¹⁴ Undertaking MRI scans without sedation during sleep in toddlers 0-4 years, however, requires extensive preparation with low success rates.^{54,55}

The Baby-CIMT group showed a decrease in affect in the parent-child relationship compared with the Baby-BIM group, where affect remained stable. Both groups showed an increase in child involvement or parent-reported infant initiation and leading of interactions, as well as an increase in parent-reported parental hostility. In both cases this may simply be an effect of development.

The REACH trial is the largest RCT to date to examine the effectiveness of very early intervention for infants at high risk of UCP commencing as young as 3-9 months and to directly compare equal doses of Baby-CIMT and Baby-BIM. A strong

feature was that all children demonstrated at least an initial 3-point difference between hands on the HAI so that clinical signs of UL asymmetry were verified before randomization. This endeavored to minimize the number of children without CP at 24 months of corrected age. Nonetheless, at 24 months, only 74% of children recruited were diagnosed with UCP. This proportion of children with normal outcomes (16.4%) has been noted in other early intervention studies.^{8,56} Whether these children had an early brain lesion that evolved or resolved by 24 months of corrected age as the result of early intervention is unknown. All children will be further followed-up at 4-6 years of age in our School Readiness study.⁵⁷ Our REACH study addressed limitations of previous studies by comparing equal dosages of intervention in both groups.⁸ In several study sites, the same therapist delivered intervention to both groups; regardless, fidelity was strong and consistent,⁴⁵ so that contamination was minimized. For both groups, the less impaired hand improved and there were no other adverse events.⁵⁸

Both Baby-CIMT and Baby-BIM home-based programs are feasible and effective treatments for improving hand function commencing at 3-9 months of corrected age in infants at high risk of UCP. Although both interventions were effective, choosing which intervention to use, and when to commence intervention, requires further consideration. Some factors for consideration include the goals of intervention, the family and therapist preferences and skills. The coaching approach used by therapists to guide the parents was successful and led to high parent engagement and enactment.

The use of the HAI and 4 defined ability levels was used to guide commencement and progression of the intervention was a strength and has clinical applicability. Each level of ability on the HAI can be used to guide the commencement and focus of therapy, for example, level 1 is reaching and pre-grasp; level 2 focused on stabilizing grasp; and level 3 focuses on changing grasp and manipulation of objects. The HAI ability levels can be used to guide the right level to commence the therapy and also how quickly to increase the level of challenge as the child gains further hand skills.

Future studies should use early MRI and asymmetry of segmental movements of fingers and wrists on Motor Optimality Score-Revised (MOS-R) followed by asymmetries on the HINE (>5 asymmetries) to identify infants with early asymmetric brain lesions who are likely to progress to UCP.⁵⁹ A greater understanding of the impact of lateralized or bimanual approaches soon after the brain lesion requires careful evaluation,⁶⁰ using semiquantitative classification of the brain injury⁶¹ analysis of cortical thickness,⁶² diffusion MRI⁶³ to elucidate brain structure and function relationships that may lead to superior outcomes. Future studies should also consider a hybrid approach combining Baby-CIMT and/or Baby BIM in an adapted trial design.

A potential limitation of our study was that the sample size was not as proposed ($n = 96/144$) in our original protocol.¹⁵ The study concluded recruitment prematurely because of the COVID-19 pandemic. The sample size recruited 96 of 144

(67% of anticipated) allowed detection of a between-group difference of 3.5 HAI impaired EaHS units (compared with 2.8 units originally). Our sample size was the largest in children with UCP² for a clinical trial in this age range.¹¹ At this study's commencement, there were no studies commencing at <9 months of age using the HAI, a recently developed tool. On the basis of recent studies of HAI with a SDD of 3 HAI units and 2 EaHS, our sample achieved clinically and statistically important changes. A limitation of the HAI was that the lack of validation beyond 12 months of corrected age; however, the developers support its utility up to 15 months of corrected age. We did not have a true control group, as it would have been unethical to withhold active intervention during a period of greatest neuroplasticity.⁶⁴ A "therapy-as-usual" group not including CIMT and/or BIM also was considered not feasible or ethical, as CIMT/BIM are best practice.

In conclusion, this large multicenter single-blind RCT found that Baby-CIMT was not superior to Baby-BIM on improving early hand function. Both interventions supported the development of hand function, were safe, feasible, and effective in infants with early asymmetric brain lesions commenced at 3-9 months of corrected age. Parents and therapists could implement either Baby-CIMT or Baby-BIM to improve UL use on the basis of family, therapist factors, and clinical reasoning. There was some evidence that infants who commenced intervention earlier at 3-6 months of corrected age had faster improvements on the HAI than those who commenced later at 7-9 months of corrected age; however, this needs to be explored further. Further research is needed with earlier commencement of intervention (<4 months PTA) and longer-term follow-up at 4-5 years. The REACH trial used principles of use-dependent neuroplasticity.⁶⁵ Intervention commenced early, targeted infants at greatest risk of UCP, the content specifically promoted use of the hemiplegic hand and/or bimanual hand skills and interventions were child active with minimal guidance. Interventions commenced at the right level of ability (based on HAI scores), were regularly incremented to optimize motor learning with an appropriate level of challenge being "not too hard nor too easy" using play-based activities that were motivating (demonstrated by high adherence). ■

CRedit authorship contribution statement

Roslyn N. Boyd: Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Susan Greaves:** Writing – review & editing, Supervision, Methodology, Investigation, Funding acquisition, Conceptualization. **Jenny Ziviani:** Writing – review & editing, Supervision, Methodology, Investigation, Funding acquisition, Conceptualization. **Iona Novak:** Writing – review & editing, Investigation, Funding acquisition. **Nadia Badawi:** Writing – review &

editing, Investigation, Funding acquisition, Conceptualization. **Kerstin Pannek:** Writing – review & editing, Methodology, Funding acquisition, Conceptualization. **Catherine Elliott:** Writing – review & editing, Supervision, Funding acquisition. **Margaret Wallen:** Writing – review & editing, Methodology, Funding acquisition. **Catherine Morgan:** Writing – review & editing, Supervision, Methodology, Funding acquisition. **Jane Valentine:** Writing – review & editing, Investigation, Funding acquisition. **Lisa Findlay:** Writing – review & editing, Methodology, Funding acquisition, Conceptualization. **Andrea Guzzetta:** Writing – review & editing, Methodology, Investigation, Funding acquisition, Conceptualization. **Koa Whittingham:** Writing – review & editing, Supervision, Investigation, Funding acquisition. **Robert S. Ware:** Writing – review & editing, Visualization, Software, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Simona Fiori:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Nathalie L. Maitre:** Writing – review & editing, Supervision. **Jill Heathcock:** Writing – review & editing, Supervision. **Kimberley Scott:** Writing – review & editing, Supervision, Investigation, Data curation. **Ann-Christin Eliasson:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Leanne Sakzewski:** Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of Competing Interest

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Full ethical approvals for this study have been obtained from the Children's Health Queensland Hospital and Health Service Human Research Ethics Committee (HREC/14/QRCH/376: ethical review provided for 20 sites: Queensland Children's Hospital, Royal Brisbane and Women's Hospital, Mater Mothers' Hospital, Gold Coast University Hospital, Sunshine Coast University Hospital, Nambour General Hospital, The Children's Hospital at Westmead, Children's Hospital Randwick, Westmead Hospital, Royal North Shore Hospital, Liverpool Hospital, Nepean Hospital, Royal Prince Alfred Hospital, Royal Women's Hospital, St George Hospital, Blacktown Hospital, Campbelltown Hospital, John Hunter Children's Hospital, Royal Children's Hospital, and Monash Medical Centre), Medical Ethics Committee of The University of Queensland (2015000013), Cerebral Palsy Alliance Ethics Committee (2015-01-02), and the Princess Margaret Hospital Human Research Ethics Committee (2015023EP: ethical review provided for 2 sites: Princess Margaret Hospital for Children and King Edward Memorial Hospital for Women). Recruitment was conducted at in Queensland at the Queensland Children's Hospital (QCH), Royal

Brisbane and Women's Hospital (RBWH), Mater Mothers Hospital, Sunshine Coast University Hospital (SCUH) and the Gold Coast University Hospital (GCUH); in New South Wales at Cerebral Palsy Alliance (CPA) and the Children's Hospital at Westmead, Sydney; in Victoria at The Royal Children's Hospital (RCH), and Monash Medical Centre (MMC) Melbourne; and in Western Australia at The Perth Children's Hospital and the King Edward Memorial Hospital for Women, Perth, in addition to the Australian Cerebral Palsy Register (ACPR). In the US, children were recruited at Nationwide Children's Hospital in Ohio and at the University of Minnesota. R.B. is the chief investigator (CI) and together with all the CIs S.G., J.Z., L.S., I.N., N.B., K.P., C.E., A.G., K.W., J.V., C.M., S.F., R.W., N.M., J.H., K.S., and A.C. designed, established, and achieved funding for this research study and meet criteria as study authors. C.M., M.W., A.-C.E., and L.F. contributed to study design. RNB, LS, CM, MW, SG, CE were responsible for ethics applications and reporting. R.B., L.S., I.N., C.E., and S.G. were responsible for recruitment. R.B., L.S., I.N., C.E., S.G., and C.M. supervised the data collection and implementation of the training program. R.B., K.P., and S.R. were responsible for design and implementation of the advanced brain imaging outcomes. R.B., J.Z., L.S., I.N., N.B., K.P., C.E., S.G., A.G., K.W., J.V., C.M., and R.W. took lead roles on preparation for publications on the clinical outcomes of the study. R.W. and L.S. took on a lead role of the statistical analysis for the study. R.B., L.S., and all the Chief Investigators drafted the final version of this manuscript. All authors have critically reviewed and approved the final version.

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