Do powered over-ground lower limb robotic exoskeletons affect outcomes in the rehabilitation of people with acquired brain injury?

A systematic review with meta-analysis

Authors:

Nicola Postol[1, 2, 3] Faculty of Health and Medicine, University of Newcastle, Australia (nicola.postol@uon.edu.au phone: +61 420506721)
http://orcid.org/0000-0002-2188-9078

Jodie Marquez[1, 2, 3] Faculty of Health & Medicine, University of Newcastle, Australia (jodie.marquez@newcastle.edu.au phone: +61 249212041)
orcid.org/0000-0002-9845-5788

Stephanie Spartalis[1], Faculty of Health and Medicine, University of Newcastle, Australia
(stephanie.spartalis@uon.edu.au)

Dr Andrew Bivard[2, 3], Hunter Medical Research Institute, Newcastle, Australia
(andrew.bivard@hotmail.com)

Professor Neil Spratt[1, 2, 3], Faculty of Health and Medicine, University of Newcastle, Australia
(neil.spratt@hnehealth.nsw.gov.au)
orcid.org/0000-0002-9023-6177

Affiliations:

1. Faculty of Health and Medicine, University of Newcastle, Callaghan, Australia
2. Priority Research Centre for Stroke and Brain Injury, University of Newcastle, Callaghan, Australia
3. Hunter Medical Research Institute, Newcastle, Australia

Corresponding author:

Nicola Postol
Faculty of Health and Medicine
University of Newcastle
University Drive, CALLAGHAN
NSW 2305, Australia
+61 420 506 721

Nicola.Postol@uon.edu.au

Introduction

Recent technological advances have led to the development of powered over-ground lower limb robotic exoskeletons, which offer a potentially valuable alternative mode of therapy for those with neurological conditions such as acquired brain injuries (ABI). ABI refers to any type of brain damage that occurs after birth, and includes both stroke and traumatic brain injury [1]. Recovery from ABI remains suboptimal and is one of the leading causes of chronic physical disability worldwide [1]. Conventional gait retraining techniques have been shown to produce improvements in speed and endurance [2]. However 30-40% of the ABI population continue to live with limited or no walking ability [3]. Evidence suggests that increased frequency and duration of therapy may improve walking ability, arm function and quality of life [4]. Yet for those with severe mobility impairment, high doses of therapy are not always feasible due to the high physical demands placed on the therapists. Two or more therapists may be needed to treat this kind of patient, to ensure upright posture, adjust their alignment for even weight distribution, facilitate movement and maintain safety. Powered over-ground lower limb robotic exoskeletons may have the capacity to overcome some of the challenges to the delivery of conventional neuro-rehabilitation.

Body weight support treadmill training (BWSTT) with robotic exoskeletons has been used in research and clinical practice for many years but has not consistently demonstrated superiority for improvements in gait function over conventional treatment methods in all people with ABI [5-8]. Electromechanical gait assistance devices, such as the Lokomat, which is paired with a treadmill, and the Gait Trainer, have been criticized for being too passive and limiting variance in movement, and visuospatial inputs [9]. Considering these factors, there may be less potential for neuroplasticity with treadmill based robotics, than with devices which offer treatment in a variety of settings and over varied surfaces [5].

In recent years various powered over-ground lower limb robotic exoskeletons have been developed [10]. One of the most reported devices is the Hybrid Assistive Limb (HAL). This robotic suit, which has both a single and double leg version, enables gait training via either voluntary drive using muscle activity detected on the skin surface or through detection of weight shifting and input pressure sensors in the shoes [5]. Other exoskeletons currently available include, but are not limited to, the Stride Management Assist (SMA) [11], Ekso [12], the Tibion leg, also known as the Alter G [13], H2 [14], Indego [15], REX [16] and ReWalk [17]. Published research with each of these devices is limited, and primarily conducted in the spinal cord injury population.

Since 2011, the potential of powered over-ground lower limb exoskeletons in people with ABI has begun to gain research interest. A systematic review is timely, in order to evaluate the potential value of exoskeletal therapy to the ABI population, to direct future research, and determine the suitability of integrating these devices into rehabilitation protocols, particularly given the very high cost of purchase which ranges from $77,000-160,000 USD [15]. Our primary aim was to determine the effect of lower limb robotic exoskeletons on neuromuscular function in people with ABI. In addition, secondary outcomes of interest were quality of life, mood, acceptability, and safety.

Method

Identification of studies:

This review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [18]. A comprehensive literature search was undertaken to locate all eligible published studies. The principal search was conducted in July 2017. Electronic searches of MEDLINE, CINAHL, PsycINFO, Embase, Cochrane Library, Scopus and PEDro were performed using over 50 medical subject

headings and key terms for the device types and ABI, then combined to locate relevant studies. The full search strategy was adjusted as required for each database. No methodological filter was used for the study design and no time limit was applied to the search in order to maximize detection. Duplicates were removed manually. Based on title, abstract and inclusion criteria, one author (N.P.) retrieved and reviewed the relevant studies after which two authors (N.P. and S.S.) independently evaluated the remaining studies for inclusion according to the agreed criteria. Any discrepancies regarding inclusion were resolved by a third researcher (J.M.). Two authors (N.P. and S.S) worked together to extract the data from each paper. In addition, the reference lists of all included articles were hand searched for further eligible studies.

Selection of studies:

Studies were eligible if they involved (1) adults over the age of 18 years with a diagnosis of ABI, irrespective of the time since ABI and level of disability (2) a powered over-ground lower limb robotic exoskeleton for at least one joint (3) over-ground treatment with or without body weight support (4) full text publication in English. Studies were excluded for not meeting the intervention criteria (treadmill-based or only one treatment session included) or if the study was a review, abstract, incomplete trial, outcome measures were not provided, data was replicated from a previous study, or the study focused on the engineering of the device.

Quality assessment:

The methodological quality of the studies was assessed using the Downs and Black checklist. This tool was chosen as it has been validated to assess both randomised and non-randomised studies [19]. The checklist involves 27 ‘yes’ or ‘no’ questions across five domains to provide an overall numeric score for study quality out

of a possible 27 points. In line with previous authors [20], the tool was modified, to simplify the scoring for question 27 dealing with statistical power. This question was adapted to a choice of either one or zero points depending on whether there was sufficient power to detect a clinically important effect. The scores for each study were determined independently by two researchers (N.P and S.S), with any disagreement resolved by a third researcher. The quality assessment, in addition to further criteria, such as consistency of results, precision of effects, and generalisability, were then used to grade the evidence for each outcome, as per the recommendations of the National Health and Medical Research Council, using the Grading of Recommendations Assessment Development and Evaluation (GRADE) classification [21,22]. This evaluation tool is widely accepted as the most effective method of linking evidence-quality evaluations to clinical recommendations.

Interventions:

The intervention of interest was lower limb exercise facilitated by a robotic device. This included when the device was used as an adjunct to routine therapy or when used in isolation. The robotic device could be from any manufacturer or design but was required to be powered. Studies examining the use of robotics purely in treadmill training were excluded due to their lack of variability of gait, an essential challenge of over-ground walking [9]. Studies were included regardless of training dosage, unless only one treatment session was used. This intervention was compared to controls of conventional therapy, alternative robotics, sham or no intervention.

Outcome measures:

The primary outcome measure of interest in this review was change in neuro-motor function related to the lower limbs, such as gait and balance. This included any

validated measure of function such as: 10 metre Walk Test (10mWT), 6 Minute Walk Test (6MWT), Timed Up and Go (TUG), sit-to-stand, Functional Reach, and Berg Balance Scale (BBS). Secondary measures of interest were quality of life, mood, acceptability, and safety.

Data analysis:

Data for assessing study quality, descriptive data and quantitative data for calculation of effect size were extracted by two authors collaboratively (N.P. and S.S) and recorded in a standardised table developed by the research team. This included information about the sample (sample size, age of participants, classification/type of device and dropout rate), the intervention (device, dosage etc.) and outcomes. Where published data were insufficient, or the study included a sample of participants with different conditions, authors were contacted and requested to provide additional data.

Where possible, meta-analyses were conducted to examine effect sizes of robotic exoskeleton usage compared to the control condition. Where the outcome measure was the same across studies, the mean difference (MD) and 95% confidence interval (CI) were reported. Where the measurement tool for the same outcome was different, the effect size was calculated using the standardised mean difference (SMD) to allow for comparison across studies. In the instance where an increased score reflected improvement, the score was multiplied by -1, so that for all outcomes in the review a positive change score post intervention reflected an improvement, in accordance with Cochrane convention [23]. Inter-trial heterogeneity was quantified using the I^2 statistic. Trials in the meta-analysis were considered to have low statistical heterogeneity if I^2 was equal or less than 25% [24], in which case a fixed-effect model was used. If I^2 was greater than 25%, a random effects model was used to allow for

inter-trial heterogeneity [23]. The Cochrane statistical package, Review Manager 5 (RevMan 2008) was used for statistical analyses.

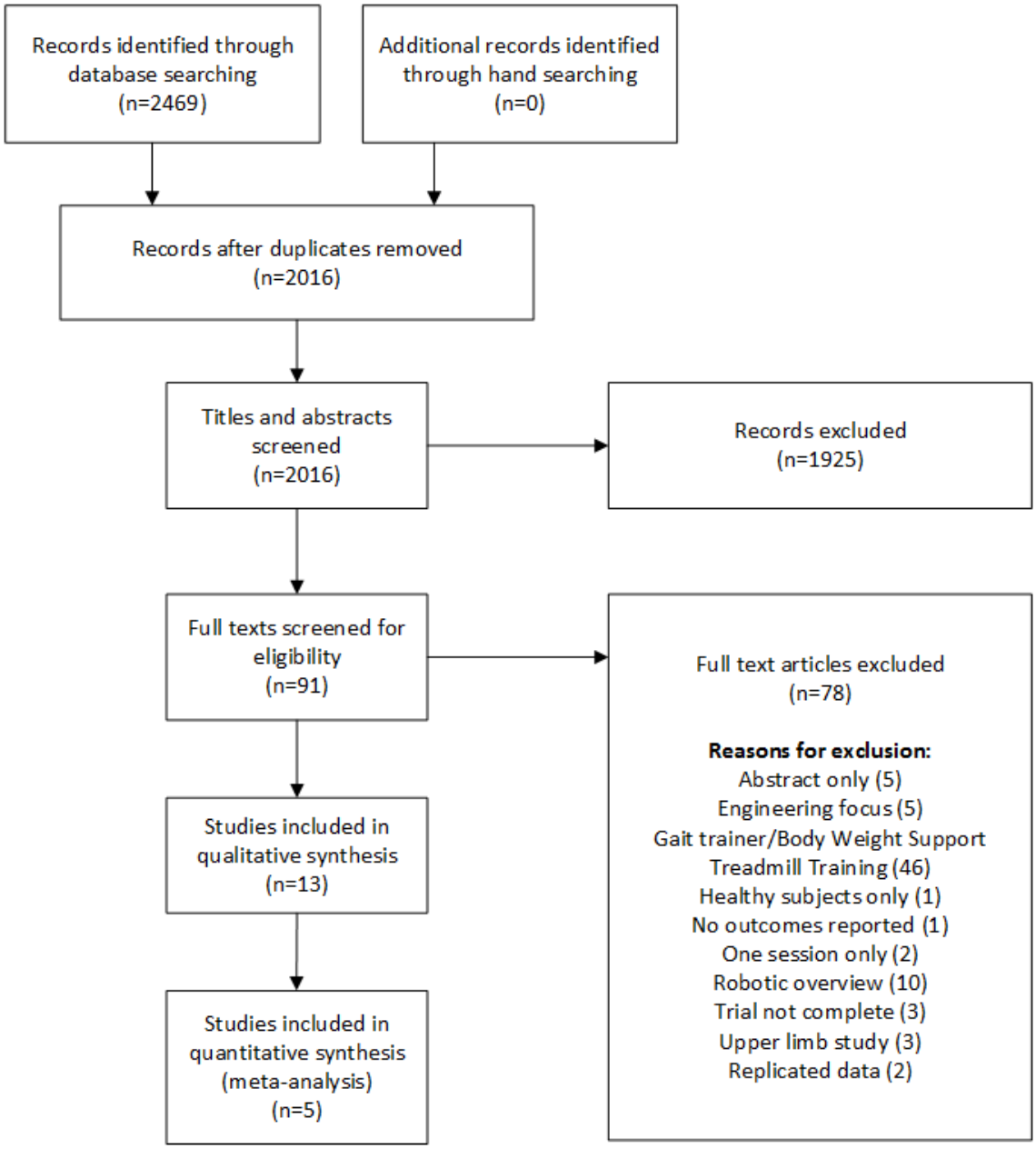
The protocol for this systematic review was registered in Prospero in March 2017 (Reference Number: CRD42017058734).

Results

Flow of studies through the review

The search resulted in the identification of 2016 articles after the removal of duplicates. After review of title and abstract, 91 were deemed potentially relevant. After retrieval of full texts, an additional 78 were excluded as they did not meet inclusion criteria. This left 13 studies for inclusion in the review, as shown in Figure 1. Five of these studies had data which could be included in meta-analysis.

Figure 1: Flow of studies through the review



Characteristics of Studies

Quality

The mean Downs and Black score of the 15 included studies was 15.6 out of a total of 27 (range: 10 – 23), as shown in Figure 2. The overall methodological quality

Figure 2: Downs and Black Quality Assessment Summary

Downs and Black Criteria	Bortole et al. (2015)	Buesing et al. (2015)	Byl et al. (2017)	Kawamoto et al. (2013)	Kubota et al. (2013)	Li et al. (2015)	Ogata et al. (2015)	Stein et al. (2014)	Ueba et al. (2012)	Watanabe et al. (2017)	Wong et al. (2011)	Yoshikawa et al. (2017)	Yoshimoto et al. (2015)
Item 1: Clear aim	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Item 2: Outcomes described	×	✓	✓	✓	✓	✓	✓	✓	×	✓	✓	✓	✓
Item 3: Subjects described	×	✓	✓	✓	✓	✓	✓	✓	✓	×	✓	✓	✓
Item 4: Intervention described	✓	✓	✓	✓	✓	✓	×	✓	×	✓	✓	✓	✓
Item 5: Principal confounders	×	✓	×	×	×	×	×	✓	×	✓	×	×	✓
Item 6: Main findings described	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Item 7: Random variability estimated	×	✓	×	✓	✓	×	×	✓	×	✓	×	✓	✓
Item 8: Adverse events reported	✓	✓	✓	✓	✓	×	✓	✓	✓	×	✓	×	✓
Item 9: Characteristics of those lost-to-follow up described	✓	✓	✓	✓	✓	✓	UTD	✓	✓	✓	✓	✓	✓
Item 10: Actual probability values reported	×	✓	×	✓	✓	×	✓	✓	✓	✓	×	✓	✓
Item 11: Potential subjects representative of population	UTD	✓	×	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Item 12: Included subjects representative of population	×	×	×	×	✓	×	✓	✓	×	✓	×	✓	×
Item 13: Staff/place/facilities representative of treatment	×	✓	×	✓	✓	✓	✓	×	✓	✓	×	✓	✓
Item 14: Blinding of subjects	×	✓	×	×	×	×	×	×	×	×	×	×	×
Item 15: Blinding of assessors	×	✓	×	×	×	×	×	✓	×	×	×	×	×

Item 16: Planned analyses clear	×	×	×	×	×	×	×	×	✓	×	×	×	×
Item 17: Similar follow-up period	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Item 18: Appropriate statistics	×	✓	×	✓	✓	×	✓	✓	✓	✓	×	✓	✓
Item 19: Compliance reliability	✓	✓	✓	✓	×	✓	✓	✓	✓	✓	✓	✓	✓
Item 20: Accurate outcome measures	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Item 21: Subjects recruited from same population	UTD	✓	UTD	✓	✓	✓	✓	UTD	×	✓	UTD	✓	✓
Item 22: Same recruitment time period	UTD	UTD	UTD	UTD	✓	UTD	✓	UTD	UTD	UTD	UTD	×	UTD
Item 23: Randomisation	×	✓	×	×	×	×	×	✓	×	✓	×	×	×
Item 24: Intervention concealment	×	✓	×	×	×	×	×	×	×	×	×	×	×
Item 25: Adjustment for confounding in analysis	✓	✓	×	UTD	×	×	×	✓	✓	×	×	×	✓
Item 26: Loss to follow-up taken into account	✓	✓	✓	✓	×	✓	UTD	×	UTD	×	✓	×	✓
Item 27: Sufficient power	×	×	×	×	×	×	×	×	×	×	×	×	×
TOTAL SCORE	10	23	11	17	17	13	15	19	14	17	12	16	19

Legend: UTD – Unable to determine (0 points); ✓ - reported (1 point); × **-** not reported (0 points)

was therefore rated as 'fair', according to previously described criteria [25]. Six studies used a controlled study design [11,26-30]. Three of these randomly allocated participants [11,26,27] and only one study [11] reported concealment of allocation. One study [11] reported blinding participants to the intervention they received and two studies blinded the assessors [11,26]. Six studies reported dropouts [11,26,27,30-32], and of these, four had more than a 15% loss of participants by completion of the study [26,27,31,32].

Participants

The 13 studies included a total of 322 participants ranging from 18 to 87 years of age (mean 59.4). The majority were male (59.4%) and 91.9% of the total sample in this review had experienced a stroke. One study recruited participants with a variety of conditions, 52.6% of them being people with ABI, 34.2% of the participants had a different neurological condition, and the rest had musculoskeletal conditions [31]. Time since ABI varied across the spectrum of chronicity (mean = 3.1 years, range: one week – 15 years). Using Bernhardt et al's classification of stage of recovery [33], nine studies [11,14,26,28,31,34-37] included participants in the chronic phase (n = 159; 49.3% of the sample), one study [30] included those in the late subacute phase (n = 18; 5.5% of the sample), and three studies included early subacute participants [27,29,32] (n = 146; 45.2% of the sample). Four studies [26,28,34,36] recruited participants who were independently mobile prior to the intervention (n = 48, 15.3%), whilst other studies [30,31,37] recruited participants who required physical assistance or the use of a mobility aid, such as a walking stick or frame (n = 72, 23%). The remainder had participants with mixed abilities, or did not specify. Seven out of the 13 studies (n=236; 73.3% of the sample) were conducted in Japan. The remaining studies were conducted

in the United States (n=83; 25.8% of the sample) [11,14,26,35,36] and China (n=3; 0.9% of the sample) [34]. A summary of included studies is shown in Table 1.

Intervention

The intervention was delivered using a range of exoskeletons. Seven of the 13 studies (n=236; 73.3% of the sample) investigated the use of the HAL [27-32,37]. Of these studies, three used this robotic exoskeleton unilaterally whilst the remainder used the bilateral set-up. Four studies (n=33; 10.2% of the sample) investigated the Tibion Bionic Leg [26,34-36], one study investigated the SMA (n=50; 15.5% of the sample) [11] and another the H2 exoskeleton (n=3; 0.9% of the sample) [14]. In three of the four devices (HAL, SMA and Tibion Leg), movement is initiated when the device senses the participant's muscle contraction, whereas movement in the H2 is initiated when the therapist activates the device. Dosage of therapy ranged from one to five sessions per week, and the duration of each session ranged from 20-90 minutes. The number of weeks of therapy ranged from three to eight.

Outcome Measures

Several standardised tools were used to assess neuromuscular function. These included the 6MWT (5 studies), TUG (8 studies), 10mWT or maximum walking speed over 10metres (9 studies), and BBS (8 studies). All studies assessed outcomes immediately following the intervention period. Five studies also assessed sustained effects at one or more later times: one month [26,27,35,36], two months [27] or three months [11,26,36]. Table 2 shows a summary of individual study findings.

Two studies reported analyses using different outcomes not comparable to the other included studies. Ogata et al [29] reported that the likelihood of achieving ≥110 on the Functional Independence Measure during the study in those with right intracranial haemorrhage as a subgroup of the experimental group, was higher in the HAL group

Table 1: Summary of included studies

Study	Design Country Device	Participants	Intervention description	Control Group	Outcome measures
Bortole et al. [14] 2015	OS USA H2 (2 limbs)Hips, knees and ankles actuated	*n* = 3 Mean age: 48.7 Range: 43-58 Chronic stroke Time since ABI: 2.1y M/F: 3/0	12 sessions 3 sessions per week for 4 weeks Gait training	No control	BBS, 6MWT, TUG, LE-FMA, BI (ADL), FGI.
Buesing et al. [11] 2015	RCT with follow-up. USA SMA (1 limb) Hip actuated	*n* = 50 Mean age: 61 Range: 18-85 Chronic stroke Time since ABI: 6.3y M/F: 33/17	18 sessions. 3x45 minute sessions per week for 6 weeks Gait training	Conventional therapy	Gait walking speed and other spatiotemporal gait characteristics.
Byl et al. [35] 2017	CS USA Tibion Leg (1 limb) Knee actuated	*n* = 3 Mean age: 54.3 Range: 42-62 Chronic stroke Time since ABI: 5.8y M/F: 1/2	16 sessions 1.5 hour sessions 2-4 times per week for 4 weeks STS, squats, gait training	No control	10mWT, 6MWT, TUG, 5x STS, Step length.
Kawamoto et al. [37] 2013	OS Japan HAL(2 limbs)	*n* = 16 Mean age: 61 Range: 18-84 Chronic stroke Time since ABI: 3.9y	16 sessions 2x 20-30 minute sessions per week for 8 weeks Gait training	No control	10mWT, TUG, BBS.

	Hips and knees actuated	Mobile with aid/assist M/F: 12/14			
Kubota et al. [31] 2013	OS Japan HAL (2 limbs) Hips and knees actuated	*n* = 38 Mean age: 53.2 Range: 18-81 Chronic stroke (12), TBI (2), Other neuro (13), MSK (4), other (7) Time since ABI: 9.5y Mobile with aid/assist M/F: 22/11	16 sessions 2 sessions per week for 8 weeks Standing and sitting exercises, gait training and single leg motions	No control	10mWT, TUG, Feasibility, BBS.
Li et al. [34] 2015	CS China Tibion Leg (1 limb) Knee actuated	*n = 3* Mean age: 58.7 Range: 53-62 Chronic stroke Time since ABI: 2.6y Independently mobile M/F: 1/2	15 sessions 5x 50 minute sessions per week for 3 weeks Transfers, mobility and gait training	No control	BBS, LE-FMA, FMA, spatiotemporal parameters of gait.
Ogata et al. [29] 2015	CT Japan HAL (2 limbs) Hips and knees actuated	*n = 91* Mean age: 64.5 Range: 57-75 Early sub-acute stroke Time since ABI: 7 days M/F: 48/43	3-6 sessions Description of therapy not provided	Conventional therapy	BI, FIM, GCS.

Stein et al. [26] 2014	RCT with follow up. USA Tibion Leg (1 limb) Knee actuated	*n = 24* Mean age: 57.1 Chronic stroke Time since ABI: 5.7y Independently mobile M/F: 17/7	18 sessions 3x 50 minute sessions per week for 6 weeks Transfers, mobility and stair practice	Relaxation/ meditation, self-stretching, range of motion exercises	10mWT, 6MWT, TUG, 5x STS, Romberg test, BBS, CAFE, EFAP.
Ueba et al. [32] 2012	OS Japan HAL (2 limbs) Hips and knees actuated	*n = 22* Mean age: 66.6 Early sub-acute stroke M/F: 7/15	3-5 sessions Description of therapy not provided	No control	Feasibility and safety.
Watanabe et al. [27] 2017	RCT with follow up. Japan HAL (1 limb) Hip and knee actuated	*n = 33* Median age: 66.9 (HAL), 76.3 (control) Early sub-acute stroke Time since ABI: 52.6 days M/F: 16/8 (analysed)	12 sessions 3 session per week for 4 weeks Mobility practice	Mobility practice	FAC, MWS, stride, cadence, 6MWT, TUG, LE-FMA
Wong et al. [36] 2011	CS USA Tibion Leg (1 limb) Knee actuated	*n = 3* Mean age: 54.7 Range: 45-73 Chronic stroke Time since ABI: 2.9y Independently mobile M/F: 2/1	18 sessions 3x 45 minute sessions per week for 6 weeks Transfers, static and dynamic balance, gait and mobility on stairs	No control	BBS, Romberg test, 6MWT, 10mWT, TUG, 5x STS, EFAP, CAFE 40.

Yoshikawa et al. [30] 2017	CT Japan HAL (1 limb) Hip and knee actuated	*n = 18* Mean age: 60.6 Late sub-acute stroke Time since ABI: 131.1 days Mobile with aid/assist M/F: 11/5	20-25 sessions 4-5 sessions per week for 5 weeks Mobility practice	Conventional therapy	MWS, FAC, BBS, SWS, FIM, LE-FMA
Yoshimoto et al. [28] 2015	CT Japan HAL (1 limb) Hip and knee actuated	*n = 18* Mean age: 65.2 Chronic stroke Time since ABI: 7.2y Independently mobile M/F: 13/5	8 sessions One 20 minute session per week for 8 weeks Mobility Practice	Conventional therapy	10mWT, TUG, BBS, FRT

Legend: **ABI** – Acquired Brain Injury, **ADL** – Activities of Daily Living, **BBS** – Berg Balance Score, **BI** – Barthel Index, **CAFE** – California Functional Evaluation, **CS** – Case series, **CT** – non-Randomised Controlled Trial, **EFAP** – Emory Functional Ambulation Profile, **F** – Female, **FAC** – Functional Ambulation Category, **FGI** – Functional Gait Index, **FIM** - Functional Independence Measure, **FMA** – Functional Motor Assessment, **FRT** – Functional Reach Test, **GCS** – Glasgow Coma Scale, **HAL** – Hybrid Assistive Limb, **LE-FMA** - Lower Extremity Fugl-Meyer, **M** – Male, **MWS** - Maximum Walking Speed, **OS** – Observational, **PCI** – Physiological Cost Index, **6MWT** – Six Minute Walk Test, **SMA** – Stride Management Assist, **STS** – Sit-to-Stand, **SWS** – Self-selected Walking Speed, **10mWT –** Ten Minute Walk Test, **TUG** – Timed Up and Go,

Table 2: Included studies: Summary of findings

Study	Outcome measures	Pre-post intervention comparison for robotic group		Between robotic and control group comparison	
		mean % change	p-value	mean change% difference	p-value
Bortole et al. [14] 2015	BBS	1.3%	N/R	No control	
	TUG	8.7%			
	6MWT	0.6%			
Buesing et al. [11] 2015	10mWT	29.1%	N/R	6.4%	0.243
Byl et al. [35] 2017	TUG	8.3%	N/R	No control	
	6MWT	27.7%			
	10mWT	35.7%			
Kawamoto et al. [37] 2013	BBS	11.8%	0.004*	No control	
	TUG	1%	0.551		
	10mWT	9.8%	0.031*		

Kubota et al. [31] 2013	BBS TUG 10mWT	5.7% 17.2% 17.3%	0.059 0.057 <0.001*	No control	
Li et al.[34] 2015	BBS	8.3%	N/R	No control	
Ogata et al. [29] 2015	No comparable outcomes reported				
Stein et al. [26] 2014	BBS TUG 6MWT 10mWT	5.4% -17.6% 14.8% 12.8%	N/R	5.8% -38% -0.3% -30.2%	0.04* 0.16 0.91 0.13
Ueba et al. [32] 2012	No comparable outcomes reported				
Watanabe et al. [27] 2017	TUG 6MWT 10mWT	103% 69.6% 51.8%	N/R	40.1% 37.9% 16.2%	0.413 0.810 0.975
Wong et al.	BBS	13%	N/R	No control	

[36] 2011	TUG 6MWT 10mWT	28% 7.6% 5.7%			
Yoshikawa et al. [30] 2017	BBS 10mWT	5.2% 23.3%	N/R	0% 18.7%	0.125 0.040*
Yoshimoto et al. [28] 2015	BBS TUG 10mWT	13% 47.7% 53.8%	<0.001* <0.001* <0.001*	12.7% 48% 58.6%	No p-values reported for between groups

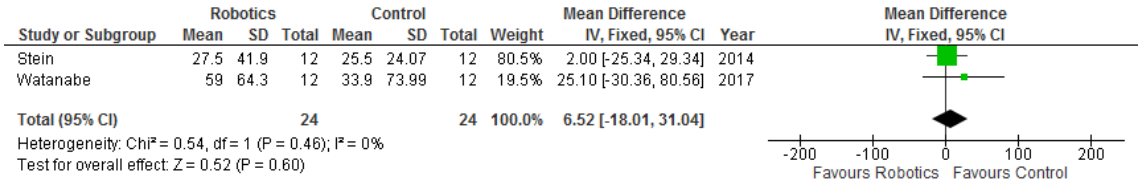
Legend ***statistically significant**
N/R – Not reported

compared to control (P=0.04). Ueba at al [32] reported subjective improvement in posture for two participants out of 22, but provided no statistical analysis.

Effect of Exoskeletal Therapy on Mobility: Endurance

Of the five studies which reported outcomes for endurance (assessed by distance walked on the 6MWT) three studies were non-controlled so were unable to be included in the meta-analysis. The pooled analysis of the two remaining studies (n = 48) [26,27] demonstrated that exoskeletal therapy did not significantly improve endurance, when compared to control therapy (MD = 6.52 metres, CI = -18.01, 31.04, P = 0.60, $I^2 = 0\%$), as shown in Figure 3. Both studies conducted follow-up assessments three months after the intervention. However, when these data were pooled they also showed no long-term benefit of exoskeletal therapy (MD = 18.11, CI = -11.44, 47.67, P = 0.23, $I^2 = 0\%$). For both these analyses the point estimate favoured the control therapy. Three non-controlled studies [14,35,36] reported improvements in endurance outcomes post-exoskeletal therapy when compared to baseline (mean change 18.1m, range -115 – 103m).

Figure 3: Effect of exoskeletal therapy on endurance



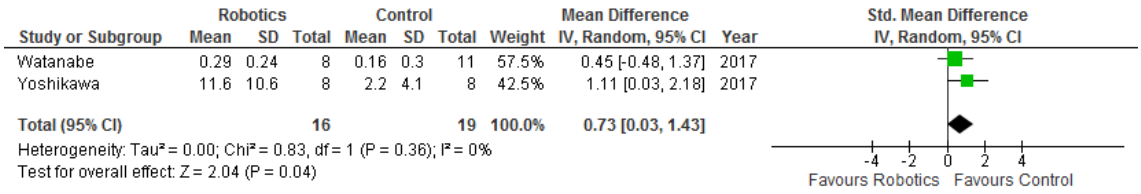
Effect of Exoskeletal Therapy on Mobility: Walking Speed

Of the nine studies using the 10mWT or maximum walking speed (MWS) as a measure of walking speed, four were non-controlled so could not be included in the meta-analysis. The sample for the pooled analysis of the five remaining studies (n =

127) [11,26-28,30] was very heterogenous (I^2 = 86%). Therefore the results of this cannot be accurately interpreted (SMD = 0.93, CI = -0.17, 2.02, P = 0.10). The average change for the control groups was 0.09 m/s (range -0.04 - 0.16), compared to 0.20 m/s (range 0.05 – 0.29) in the robotic groups. Three studies (n=84) [11,26,27] provided three month follow up data. While the point estimate favoured the control, meta-analysis showed no significant long-term difference (SMD = 0.16, CI = -0.64, 0.97, P = 0.69, I^2 = 65%). The four non-controlled studies [31,35-37] which evaluated walking speed reported improvements post-exoskeletal therapy when compared to baseline (mean change -3.3 seconds, range -11.2 – 1 second).

The five controlled studies were also included in sub-analysis of the difference in walking speed for chronic and subacute stages of recovery. Subacute participants [27,30] (n = 35) improved less with exoskeletal therapy than in the control group in walking speed (SMD = 0.73, CI = 0.03, 1.43, P = 0.04, I^2 = 0%), as shown in Figure 4. Three studies [11,26,28] (n = 92) with chronic participants demonstrated no statistically significant difference (SMD = 1.03, CI = -0.81, 2.86, P = 0.27), but again this sample was too heterogenous to draw conclusions from this analysis (I^2 = 93%).

Figure 4: Effect of exoskeletal therapy on walking speed (subacute participants)



Effect of Exoskeletal Therapy on Balance:

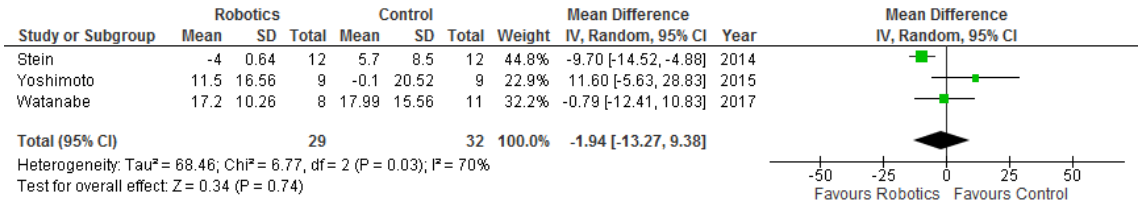
Balance was predominantly assessed using the TUG and BBS. These scales assess different aspects of balance. The TUG measures dynamic stability, whereas the

BBS assesses anticipatory and reactive components of balance [38]. For this reason, they were analysed separately.

Effect of Exoskeletal Therapy on Balance: Dynamic Stability:

Of eight studies which used the TUG as a measure of balance, five were non-controlled and therefore not included in meta-analysis. The pooled analysis of three studies [26-28] (n=61) demonstrated that the point estimate favoured exoskeletal therapy, but there was no statistically significant difference between robotic and control therapy (MD = -1.94, CI = -13.27, 9.38, P = 0.74, I^2 = 70%), , as shown in Figure 5. The five non-controlled studies with TUG data [14,31,35-37] all reported improvements post-exoskeletal therapy when compared to baseline (mean change -3.1 seconds, range -11.7 -1.9 seconds).

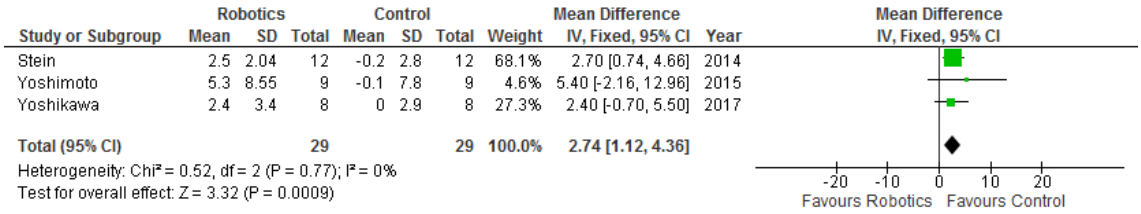
Figure 5: Effect of exoskeletal therapy on dynamic stability



Effect of Exoskeletal Therapy on Balance: Anticipatory and Reactive:

Of eight studies using the BBS, five were non-controlled and therefore not included in meta-analysis. The pooled data (n=54) from three controlled studies [26,28,30] demonstrated statistically significant improvement in favour of the control group (MD = 2.74, CI = 1.12, 4.36, P = 0.0009, I^2 = 0%), as shown in Figure 6. The five non-controlled studies [14,31,34,36,37] reported improvements post- exoskeletal therapy when compared to baseline (mean change 3.2, range 0 - 6).

Figure 6: Effect of exoskeletal therapy on anticipatory and reactive balance



Quality of Life and Mood

None of the 13 studies included in this review assessed quality of life or mood associated with the use of exoskeletal therapy.

Acceptability of Exoskeletal Therapy

Six studies reported dropouts throughout various stages of the trial [11,26,27,30-32], as shown in Table 3. Reported reasons included medical conditions, transportation issues and depression. The drop-out rate for the pooled sample was 11.5% (n=37). Four of the six studies had a greater than 15% drop-out rate [26,27,31,32], one of which had a >50% drop-out rate [27]. In total 66.7% of reported dropouts were from the robotic groups.

One study [14], with three participants, assessed usability from the participant's perspective with one question on a 10 point Likert Scale where 0 indicated "extremely hard to use" and 10 indicates "extremely easy to use". Ratings were favourable overall, with the average rating being 7.2.

Safety

Eight studies reported no adverse events throughout the intervention period [11,14,26,28,29,35-37]. One [31] documented that "a few patients developed lumbar or knee pain during the training". Another study [32] reported that 4 of 22 participants experienced orthostatic hypotension within the treatment session, which prevented one

Table 3: Summary of drop outs

Included studies that reported drop outs	Reported drop outs N (% of study sample)	Robotic drop outs	Control drop outs	Reason for drop out
Buesing et al. [11] 2015	(4) 8%	Not specified		Transportation issues and scheduling conflicts.
Kubota et al. [31] 2013	(6) 15.8%	6	0	Medical reasons (n = 4), Transportation (n = 2).
Stein et al. [26] 2014	(4) 16.7%	2	2	Medical (n = 2), fail to complete follow-up (n = 2),
Ueba et al. [32] 2012	(6) 27.3%	6	0	Depression, inappropriate shoe size, medical reasons
Watanabe et al. [27] 2017	(15) 51.5%	6	9	Medical reasons, refusal to attend, early D/C, withdrew consent.
Yoshikawa et al. [30] 2017	(2) 11%	2	0	Medical reasons (n = 1), withdrew consent (n = 1).
Total drop outs	(37) 11.5%	22 (6.9%)	11 (3.5%)	

from continuing participation in the trial. An initial diagnosis of intracerebral haemorrhage and lower Brunnstrom Recovery stages were significantly associated with the occurrence of orthostatic hypotension in this study (P = 0.007 and P = 0.033, respectively). Three studies [27,30,34] failed to comment on the presence or absence of adverse events.

Recommendations

There was consistent reporting of positive findings related to exoskeletal therapy across the studies. Eight of nine studies reported pre-post improvements in walking speed, five of five studies reported pre-post improvements in endurance, eight of eight studies reported pre-post improvements in BBS and seven of eight studies reported pre-post improvements in TUG. However, the size of the treatment effect across and within studies was variable, and when the exoskeletal and control conditions were compared, the exoskeletal treatment effect was not statistically different, or was inferior, to the control condition. Generalisability of the findings is limited due to most of the sample coming from Japan and the US (99.1%), as the 'control condition' or adjunct therapy may differ between countries, with standard dosage and mix of intervention potentially differing. Generalisability is further limited as 73.3% of the sample received therapy with the HAL device, however the findings do apply to those with varying degrees of chronicity and mobility impairment. Considering all these factors, our recommendations were rated as low strength against the use of exoskeletal therapy for endurance, walking speed and for balance as measured by TUG. Our recommendation was rated as moderate strength against the use of robotics for balance as measured by BBS. A summary is provided in Table 4.

Table 4: Recommendations for robotic therapy (GRADE)

	Robotic Exoskeletons for Acquired Brain Injury Population **Patients:** Adults with an acquired brain injury **Settings:** Primary care, community, outpatient **Intervention:** Therapy using powered over-ground lower limb robotic exoskeletons **Comparison:** Usual care, adjunct therapy, no comparison					
Outcomes **Study Design**	**Risk of bias** *Average Downs and Black score*	**Consistency of findings**	**Precision of effects** *Mean change compared to control (CI)*	**Precision of effects** *Mean change (range) non-controlled studies*	**No. of participants (no. of studies)**	**GRADE Rating of evidence** **(comments)**
Endurance (6MWT) 1 OS [14] 2 CS [35,36] 2 RCT [26,27]	14	5/5 studies reported positive findings.	MD 6.52 (-18.01, 31.04), P=0.60 Pooled effects from meta-analysis of two studies. High inter-trial homogeneity (I^2=0%) with two different research groups.	18.1 (-115 – 103m)	66 (5)	ØØOO Low (a,b,c)
Walking speed (10mWT) 2 OS [31,37] 2 CS [35,36] 2 CT [28,30]	16.8	8/9 studies reported positive findings.	SMD 0.93 (-0.17, 2.02), P=0.10 Pooled effects from meta-analysis of five studies. Low inter-trial homogeneity (I^2=86%).	0.11 (-0.1 – 0.2)	203 (9)	ØØOO Low (a,c)

3 RCT [11,26,27]						
Balance (BBS) 3 OS [14,31,37] 2 CS [34,36] 2 CT [28,30] 1 RCT [26]	15.3	8/8 studies showed positive findings.	MD 2.74 (1.12, 4.36), P=0.0009 (favoured control) Pooled effects from meta-analysis of three studies. High inter-trial homogeneity (I^2=0%) with different research groups.	3.2 (0-6)	123 (8)	ØØØO Moderate (a,d,e)
Balance (TUG) 3 OS [14,31,37] 2 CS [35,36] 1 CT [28] 2 RCT [26,27]	15.1	7/8 studies showed positive findings.	MD -1.94 (-13.27, 9.38), P=0.74 Pooled effects from meta-analysis of three studies. Low inter-trial homogeneity (I^2=70%).	-3.1 (-11.7 – 1.9)	138 (8)	ØØOO Low (a,b,c)
Legend **CS** – Case Series, **CT** – Controlled Trial, **MD** – Mean Difference, **OS** – Observational Study, **RCT** – Randomised Controlled Trial, **SMD** – Standardised Mean Difference a) treatment effect was variable, b) wide CI, c) CI crosses zero, d) lack of RCTs, e) statistical significance reached						

Discussion

This review of 13 studies (n=322), averaging fair methodological quality, has not provided sufficient evidence to support the use of these devices in the ABI population, in preference to conventional therapy. Whilst most studies report functional improvements following exoskeletal therapy, this was not superior to the control condition, and for BBS those receiving exoskeletal therapy performed significantly worse than controls. Exoskeletal therapy was generally safe, with no serious adverse events. No studies assessed effects on mood, acceptability and quality of life.

The lack of favourable findings for exoskeletal therapy may be due to the heterogeneity of the sample, as it is likely that some people with ABI may derive more benefit than others. In particular, data from one of the included studies [37], suggests that dependent ambulators benefitted from use of the HAL, while independent ambulators did not. The investigators found statistically significant improvements in the dependent ambulators for speed and BBS, and the minimum clinically important difference was also achieved for BBS [39]. Conversely, whilst statistical significance was reached for BBS in the independent ambulators, the minimum clinically important difference was not achieved for any outcome. Similar results have been found in previous research on robot-assisted gait with the Gait Trainer [40].

We were unable to undertake planned subgroup analyses of the influence of ABI severity and time since ABI, due to the lack of data. Our one sub-group analysis of walking speed found that the sub-acute group were more likely to improve with control rather than exoskeletal therapy, but heterogeneity of the sample in the meta-analysis prevented an accurate comparison with chronic participants. Further investigation into those most likely to benefit from each device, across all outcome measures, is warranted. Sub-group analysis of stage of recovery and dependence of ambulation may

make it clearer which people with ABI are likely to make clinically meaningful improvement. It is also pertinent to consider whether people with ABI who are already independently mobile can make gains with exoskeletal therapy, given that it may be too restrictive and supportive, and the inclusion of them in some studies in this review may have diluted the results.

As might be expected, there was no evidence of delayed improvement in outcomes during the months after therapy. Dosage of therapy varied and may not have been sufficient to achieve significant change, although the pooled results from the controlled studies suggest that irrespective of dosage, the control condition is equal to or better than robotics. Whilst our review has not demonstrated superior benefit of exoskeletal therapy, and there is no evidence of harmful effects, controlled trials can be justified with longer periods of therapy, in the dependent ambulators, to determine whether exoskeletal therapy can augment the benefits of repeated task-oriented practice in this sub-group, which is the current convention. Routine clinical use cannot yet be supported due to the unlikeliness of important benefits and extremely high cost. However, along with the efficacy of intervention, future research must consider the cost-benefit analysis of therapist led versus device led intervention, to be able to fully understand whether, if the outcomes are comparable in both groups, the high purchase cost can be justified, as is currently being studied in the WISE trial for those with spinal cord injury [41].

Neuromuscular function was the primary focus of the studies included in this review, but in neuro-rehabilitation there are other outcomes which merit analysis. A systematic review of the literature on exoskeletal therapy in the spinal cord injured population included outcomes such as spasticity, sensory changes, sitting posture, cardiorespiratory and psychological function, although most included studies were

analysing effects with treadmill based devices, and no meta-analysis was conducted [42]. This review could not make any assessment of the potential of exoskeletal therapy to improve these in people with ABI, and further research of these important outcomes is recommended.

We can only make cautious comments with regard to patient acceptability of exoskeletal therapy due to lack of investigation and drop-out rates in some studies. Although the overall retention rate was 88.5%, some studies had relatively high drop-out rates, adding to risk of bias, and 66.6% of the reported drop-outs overall were in the robotic groups. The studies with >15% drop-out rates were not consistent in terms of dosage of therapy or type of participant, however the study with the highest drop-out rate included participants in the early sub-acute phase of their rehabilitation, and treatment frequency was relatively high compared to other studies at three sessions per week [28]. One study which recorded multiple adverse events may be explained by the early sub-acute nature of the participants, as four of them suffered orthostatic hypotensive episodes [33]. Only one study reported patient attitudes towards exoskeletal therapy and this was via a single question. The drop-out rates and adverse events could relate to the acceptability and feasibility of this type of treatment, but are also indicative of the general health and medical stability of the ABI population. A 2016 feasibility study with spinal cord injured participants in the ReWalk found that users had high expectations of the benefit they may derive from exoskeletal therapy, and these expectations were generally not met [43]. In future research, patient acceptability needs to be a primary consideration, with questions to probe both user expectations, and perceptions of comfort, usability and safety.

Strengths and limitations

Whilst the studies were heterogenous in terms of ABI severity, stage of recovery, country of research, device used, dosage of therapy, use of control, and follow up of participants, this review does have many strengths. The search was extensive, the included studies were of fair quality, and the data have been analysed both narratively and quantitatively. There may be more benefit with these devices in more dependent ambulators, and both this, and investigation of other outcomes, warrant further research.

Conclusion

Over the past decade, several powered over-ground exoskeleton devices have emerged. This review has demonstrated that in the ABI population, there is no more benefit of these devices on neuromuscular function than with traditional therapy, and for some outcomes, analysis favours control therapy. More research is required in dependent ambulators to determine whether more carefully selected populations may derive some benefit, and whether this is different depending on stage of recovery. The cost of these devices is significant [16], and in the absence of scientific evidence demonstrating superiority over conventional treatment methods, recommendations for use in the ABI population should currently be restricted to research.

References

1. Whyte E, Skidmore E, Aizenstein, et al. Cognitive impairment in acquired brain injury: a predictor of rehabilitation outcomes and an opportunity for novel interventions. PMR. 2011; 3(601): 45-51.
2. States RA, Salem Y, Pappas E. Over ground gait training for individuals with chronic stroke: a Cochrane systematic review. J Neurol Phys Ther. 2009; 33(4): 179-186.

3. Jorgensen HS, Nakayama H, Raaschou HO, et al. Recovery of walking function in stroke patients: the Copenhagen Stroke Study. Arch Phys Med Rehabil. 1995; 76(1): 27-32.
4. (Australian) Clinical Guidelines for Stroke Management 2017 – Chapter 5 of 8: Rehabilitation [Internet]. Melboune (VIC). Stroke Foundation; 2017 Dec 8 [cited 2018 Jan 23]. Available from: htttps://www.magicapp.org/app#guideline/2146/section/25236
5. Wall A, Borg J, Palmcrantz S. Clinical application of the Hybrid Assistive Limb (HAL) for gait training – a systematic review. Front Syst Neurosci. 2015; 9: 48.
6. Kelley CP, Childress J, Boake C, Noser EA. Over-ground and robotic-assisted locomotor training in adults with chronic stroke: a blinded randomized clinical trial. Disabil Rehabil Assist Technol. 2013; 8(2):161-168.
7. Swinnen E, Beckwée D, Meeusen R, et al. Does robot-assisted gait rehabilitation improve balance in stroke patients? A systematic review. Top Stroke Rehabil, 2014, 21: 87–100.
8. Cho DY, Park SW, Lee MJ, et al. Effectiveness of robot-assisted gait training on the balance and gait of chronic stroke patients: focus on dependent ambulators. J Phys Ther Sci. 2015; 27(10): 3053-3057.
9. Wiart L, Rosychuk RJ, Wright FV. Evaluation of the effectiveness of robotic gait training and gait-focused physical therapy programs for children with cerebral palsy: a mixed methods RCT. BMC Neurol. 2016; 16: 86.
10. Harvey LA. Physiotherapy rehabilitation for people with spinal cord injuries. J Physiother. 2016; 62(1): 4-11.
11. Buesing C, Fisch G, O'Donnell M et al. Effects of wearable exoskeleton stride management assist system (SMA) on spatiotemporal gait characteristics in individuals after stroke: a randomised controlled trial. J Neuroeng Rehabil, 2015; 12(69): 101-113.
12. Spectrum. [Internet]. IEEE Spectrum; [cited 2017 May 15]. Available from: http://spectrum.ieee.org/the-human-os/biomedical/bionics/paraplegic-man-walks-in-ekso-robotic-exoskeleton-to-demo-its-killer-app.

13. AlterG. [Internet]. United Kingdom: Alter G, inc; [cited 2017 October 11]. Available from: http://www.alterg.com/products/bionic-leg/professional-physical-therapy
14. Bortole M, Venkatakrishnan A, Zhu F, et al. The H2 robotic exoskeleton for gait rehabilitation after stroke: early findings from a clinical study. J Neuroeng Rehabil. 2015; 12(54): 1-14.
15. Esquenazi A, Takaty M, Jayaraman A. Powered exoskeletons for walking assistance in persons with central nervous system injuries: a narrative review. PM&R. 2017; 9(1): 46-62.
16. REX Bionics. [Internet]. Melbourne: Rex Bionics LTD; [Cited 2017 May 20]. Available from: http://www.rexbionics.com/rex-for-clinical-use/.
17. Esquenazi A, Talaty M, Packel A, et al. The ReWalk powered exoskeleton to restore ambulatory function to individuals with thoracic-level motor-complete spinal cord injury. Am J Phys Med Rehabil. 2012; 91(11): 911-921.
18. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int J Surg. 2010; 8(5): 336-341.
19. Downs SH, Black N. Feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J Epidemiol Community Health. 1998; (52): 377-384.
20. Baschung Pfister P, de Bruin ED, Tobler-Ammann BC, et al. The relevance of applying exercise training principles when designing therapeutic interventions for patients with inflammatory myopathies: a systematic review. Rheumatol Int. 2015; 35: 1641–1654.
21. National Health and Medical Research Council. [Internet]. Australia; Commonwealth of Australia 2017; [Cited 2017 June 01]. https://www.nhmrc.gov.au/guidelines-publications/information-guideline-developers/resources-guideline-developers.
22. Schünemann HJ, Oxman AD, Vist GE, et al. Chapter 12: Interpreting results and drawing conclusions. Cochrane Handbook. 2017.

23. Higgins JPT, Green S. Cochrane handbook for systematic reviews of interventions. Version 5.1.0. The Cochrane Collaboration. 2011.
24. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003; 327: 557-60.
25. O'Connor SR, Yully MA, Ryan B, et al. Failure of a numerical quality assessment scale to identify potential risk of bias in a systematic review: a comparison study. BMC Res Notes. 2015; 8: 224.
26. Stein J, Bishop L, Stein DJ, et al. Gait training with a robotic leg brace after stroke: a randomized controlled pilot study. Am J Phys Med Rehabil. 2014; 93(11): 987-994.
27. Watanabe H, Goto R, Tanaka N, et al. Effects of gait training using the Hybrid Assistive Limb in recovery-phase stroke patients: a 2-month follow-up, randomised controlled study. NeuroRehabilitation. 2017; 40: 363-367.
28. Yoshimoto T, Shimizu I, Hiroi Y, et al. Feasibility and efficacy of high-speed gait training with a voluntary driven exoskeleton robot for gait and balance dysfunction in patients with chronic stroke: non-randomised pilot study with concurrent control. Int J Rehabil Res. 2015; 38(4): 338-43.
29. Ogata T, Abe H, Samura K, et al. Hybrid Assistive Limb (HAL) Rehabilitation in patients with acute hemorrhagic stroke. Neurol Med Chir. 2015; 55(12): 901-906.
30. Yoshikawa K, Mizukami M, Kawamoto H, et al. Gait training with Hybrid Assistive Limb enhances the gait functions in sub-acute stroke patients: a pilot study. NeuroRehabilitation. 2017; 40(1): 87-97.
31. Kubota S, Nakata Y, Eguchi K, et al. Feasibility of rehabilitation training with a newly developed wearable robot for patients with limited mobility. Arch Phys Med Rehabil. 2013; 94(6): 1080-1087.
32. Ueba T, Hamada O, Ogata T, et al. Feasibility and safety of acute phase rehabilitation after stroke using the Hybrid Assistive Limb robot suit. Neurol Med Chir. 2013; 53(5): 287-290.

33. Bernhardt J, Hayward KS, Kwakkel G, et al. Agreed definitions and a shared vision for new standards in stroke recovery research: the stroke recovery and rehabilitation roundtable taskforce. Int J Stroke. 2017; 12(5): 444-450.
34. Li L, Ding L, Chen N, et al. Improved walking ability with wearable robot-assisted training in patients suffering chronic stroke. Biomed Mater Eng. 2015; 26: 329-340.
35. Byl NN. Mobility training using a bionic knee orthosis in patients in a post-stroke chronic state: a case series. J Med Case Rep. 2012; 6: 1-5.
36. Wong K, Bishop L, Stein J. A wearable robotic knee orthosis for gait training: a case-series of hemiparetic stroke survivors. Prosthet Orthot Int. 2011; 36(1): 113-120.
37. Kawamoto H, Kamibayashi K, Nakata Y, et al. Pilot Study of locomotion using hybrid assistive limb in chronic stroke. BMC Neurology. 2013; 13: 141.
38. Dixon CJ, Knight T, Binns E, et al. Clinical measures of balance in people with type II diabetes: a systematic literature review. Gait Posture. 2017; 58: 325-332.
39. Donoghue D, Stokes EK, Murphy A et al. How much change is true change? The minimum detectable change of the Berg Balance Scale in elderly people. J Rehabil Med. 2009; 41(5): 343-346.
40. Morone G, Iosa M, Bragoni M, et al. Who may have durable benefit from robotic gait training?: a 2-year follow-up randomized controlled trial in patients with subacute stroke. Stroke. 2012; 43(4): 1140-1142.
41. Clinicaltrials.gov [Internet], United States; US National Library of Medicine [cited 2018, July 03]. https://clinicaltrials.gov/ct2/show/NCT02943915
42. Holanda LJ, Silva PMM, Amorim TC, et al. Robotic assisted gait as a tool for rehabilitation of individuals with spinal cord injury: a systematic review. J Neuroeng Rehabil. 2017; 14:126.

Benson I, Hart K, Tussler D, van Middendorp JJ.. Lower-limb exoskeletons for individuals with chronic spinal cord injury: findings from a feasibility study. Clin Rehabil. 2016; 30(1): 73-84.