TECHNOLOGY REVIEW (MINI-HTA)

LOWER LIMB EXOSKELETON FOR GAIT THERAPY

Malaysian Health Technology Assessment Section (MaHTAS)
Medical Development Division
Ministry of Health Malaysia
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EXECUTIVE SUMMARY

Background

Walking (gait) is a complex and unique motor activity that consists of three major components: movement, balance and the capacity to adapt to one's surroundings. Normal gait requires a delicate balance of multiple interacting systems, including three major afferent sensory systems, a locomotor efferent system and strict monitoring by several central nervous system structures. Gait irregularities in older people are a major source of functional impairment, lower quality of life, morbidity and even fatality due to their link to falls and resultant catastrophic fractures or head injuries. According to the clinical setting, 2.0% to 20.0% of patients were referred for mobility problems. Outpatient clinics have a functional movement issue, and 40.0% of these patients have gait abnormalities without a structural disability. Regrettably, neurological gait and balance impairments are notoriously difficult to cure. For patients with gait disorders, rehabilitation is one of the process of recovering or controlling damaged abilities. Rehabilitation aims to restore motor abilities through repeated, high-intensity and task-specific exercises. This process establishes new brain connections that enable the re-transmission of motor impulses. Over the years, numerous robotic systems have been used to rehabilitate patients by performing repeated task-specific tasks. Robotic assistive devices train patients' limbs to send and receive signals from the brain, resulting in enhanced motor function. These modern technologies, which feature interactive automation, sensors and dynamic control logic can operate with minimum involvement of physiotherapist participation. This strategy is claimed to maximise the expertise and time of physiotherapists, leading to more successful rehabilitation programs.

Objective/aim

The objective of this technology review was to assess the effectiveness, safety, organisational issue and economic implication of lower limb exoskeleton as a therapy option for patients with gait abnormality.

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Results and conclusions

The initial searches yield a total of 9,085 citations. After assessing for eligibility criteria, 19 full text articles were subsequently retrieved and included in the review, which consists of one systematic review and meta-analysis, three systematic reviews alone, 12 randomised controlled trials, two cost-effectiveness analysis studies and one budget impact analysis study. The studies were conducted mainly in United States, followed by countries in Asia Continents (Malaysia and South Korea), Europe Continents (Austria, Switzerland, Italy and United Kingdom) and Australia.

Effectiveness:

There was large and high level of retrievable evidence to suggest lower limb exoskeleton improved gait impairment regarding patient-subjective outcomes relative to those who receive placebo or any conventional rehabilitation program. Findings in general indicated that:

a. Stroke (subacute, mild and chronic)

i. Exoskeleton improved significantly in walking speed ($p<0.05$), 6-minute walking test (6MWT; $p=0.03$), gait distance ($p<0.0001$), muscle strength ($p<0.0001$) and balance ($p<0.0001$) as compared to baseline.
ii. Exoskeleton improved significantly in lower limb joint angles and forces ($p<0.05$) as compared to baseline.
iii. In severe impairment patients, the walking test favoured exoskeleton groups significantly ($p=0.0003$).
iv. In haemorrhagic stroke patients, exoskeleton showed significantly higher on balance ($p=0.029$) and daily step count ($p=0.013$) as compared to control.

v. Exoskeleton showed significant improvement in EuroQoL-5D (EQ-5D) score, Functional Ambulatory Category (FAC) score, Fugl-Meyer Assessment (FMA) scale lower-limb, Korean-modified Fall Efficacy Scale (K-FES), spatiotemporal measures and all gait symmetry as compared to the control group ($p<0.05$).
vi. Exoskeleton showed significant impact on the electromyography amplitude of paretic muscles than in control group ($p=0.04$).

b. Spinal cord injury (SCI)
i. Exoskeleton group showed the highest increase in self-selected gait speed and mean distance covered, as well as the shortest median time for timed-up-and-go, as compared to the control group.
ii. Exoskeleton dominated control intervention significantly in the ambulatory assessment.

c. Multiple sclerosis
i. Exoskeleton improved significantly in Symbol Digit Modalities Test (SDMT), thalamocortical resting-state functional connectivity, Functional Independence Measure (FIM) and Tinetti Balance Scale (TBS) ($p<0.001$) in 6 weeks.

Safety:
There was limited and high level of retrievable evidence suggesting that lower limb exoskeleton was generally safe with no device-related falls or serious adverse events, plus well-tolerated by patients during gait therapy. This device was not associated with death or hospitalisation, as well as has been approved by United States of Food and Drug Administration (US FDA) for medical purposes and registered in Medical Device Authority Malaysia.

Economic implication:
i. In incomplete SCI, exoskeleton was not the most cost-effective alternative for an additional quality-adjusted life year (QALY) at any willingness-to-pay (WTP) level.
ii. In complete SCI, when WTP exceeds $10,000 USD per QALY, exoskeleton showed the highest likelihood of being cost-effective. When comparing locomotor techniques in patients with complete SCI, 75.0% of simulations showed that exoskeleton produced the greatest net gain.
iii. In patients with hip fracture, the exoskeleton was expected to be cost-effective in cardiovascular and dementia patients under the age of 75.
iv. In terms of leasing the device, the exoskeleton was not cost-effective until it increased patients' health-related quality of life (HRQoL) by 25.0% and had a risk ratio of falling of 0.625. Meanwhile, in terms of purchasing to be considered cost-effective, the device should increase patients' HRQoL by 48.0% and decrease secondary hip fracture by 50.0%.
v. Cost-savings would be achieved when the robotic exoskeleton life was prolonged to eight years.

Partial Economic Evaluation:
i. The total cost of a typical 27-session RAGT course is RM5,449.33. In contrast, the total cost for 27 sessions of traditional treatment is RM355.32. When compared to standard treatment, RAGT incurs an additional cost of RM5,094.01.
ii. The incremental cost-effectiveness ratio (ICER) was determined to be RM16,980.04 per efficacy unit, implying that for every one-unit increase in efficacy, RAGT costs an extra RM16,980.04 when compared to conventional treatment.
iii. The number of sessions per year and their efficacy (increasing the number of sessions improves cost-effectiveness), have the largest impact on the ICER, whereas human

resource expenses have little influence (staffing modifications can result in considerable ICER improvements).

Organisational issues:
Prior to implementing exoskeletons, it should follow the principles and hierarchy of preventive measures, ensuring that their use first and foremost helps to eliminate or control the identified risk factor. Furthermore, their introduction in the workplace does not create new risks for users or third parties, or elicits a rejection response from those who must use them. Introducing new technology into the workplace needs a thorough evaluation of Occupational Safety and Health (OSH) by all parties concerned. The Framework Directive (89/391/EEC) specifies a design that prioritises human comfort and well-being. Depending on the technology, personnel must receive sufficient training to use exoskeletons successfully and safely. This training may need time and resources. Exoskeletons require continual maintenance to function properly. This scenario might result in increased expenditures and operational complexity.

Conclusion:
The comparison between lower limb exoskeletons and conventional rehabilitation highlights both the benefits and challenges associated with each approach. Lower limb exoskeletons can significantly enhance mobility and functional independence, allowing patients to engage in more active rehabilitation with no serious adverse events. They provide consistent support and can facilitate intensive training, which may accelerate recovery for some patients, especially in stroke, SCI and multiple sclerosis patients. However, these devices come with high upfront costs, maintenance expenses and the need for specialised training for both users and clinicians.

Methods
A systematic review was conducted. Review protocol, search strategy and literature search was developed by the main author related to lower limb exoskeleton for gait therapy. The following electronic databases were searched through the Ovid interface: MEDLINE® All <1946 to 12th July 2024. Comparative searches were run in EMBASE, Cochrane Library, PubMed, USFDA and INAHTA database while further articles were retrieved from reviewing the bibliographies of retrieved articles. Only articles on humans were included in the review. There was no language restriction in the search. The most recent search was carried out on 12th July 2024.

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ABBREVIATIONS

6MWT	6-minute walking test
ADL	Activities of daily living
BBS	Berg Balance Scale
BWSOGT	Body weight-supported overground training
BWSTT	Body weight-supported treadmill training
CI	Confidence interval
EQ-5D	EuroQoL-5D
FAC	Functional Ambulatory Category
FIM	Functional Independence Measure
FMA	Fugl-Meyer Assessment
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
K-FES	Korean-modified Fall Efficacy Scale
MA	Meta-analysis
MAS	Modified Ashworth Scale
OSH	Occupational Safety and Health
QALY	Quality-adjusted life year
RAGT	Robot-assisted gait training
RCT	Randomised controlled trial
ROB	Risk of bias
SCI	Spinal cord injury
SD	Standard deviation
SDMT	Symbol Digit Modalities Test
SMD	Standardised mean difference
SR	Systematic review
TBS	Tinetti Balance Scale
US FDA	United States of Food and Drug Administration
WTP	Willingness-to-pay

1.0 BACKGROUND

Walking (gait) is a complicated and distinctive motor behaviour made up of three main components: locomotion, balance and the ability to adjust to the surroundings. Normal gait necessitates a delicate balance between multiple interacting systems, including three major afferent sensory systems (visual, vestibular and proprioceptive senses), a locomotor efferent system (including nerves and muscles), and strict surveillance by several central nervous system structures. Gait abnormalities in older individuals are a major cause of functional impairment, reduced quality of life, morbidity and even mortality because to their association with falls and subsequent catastrophic fractures or head trauma.[1]

In adult, a gait issue can be the first sign of a variety of neurologic illnesses. Important epidemiological data on various gait disorders in 488 people have been provided by the Bruneck study, which follows a representative sample of the population of a small region in northern Italy over an extended period of time. Among those between the prevalence of gait and balance abnormalities rises with age, from 10.0% between 60 and 69 years to more than 60.0% in those over 80 years.[2] According to the clinical setting in the Bruneck study, 2.0% to 20.0% of patients referred to movement disorders outpatient clinics have a functional movement disorder,[3] and 40.0% of these patients exhibit gait problems without a structural impairment.[4,5] In two thirds of those affected by any gait disorder, the cause was neurological and in approximately one half, the cause was non-neurological.[2] In Malaysia, there are several gait rehabilitation centres and clinics that focus on improving mobility and gait for individuals recovering from injuries or dealing with neurological conditions, which are National Stroke Association of Malaysia (NASAM), SOCSO Rehabilitation Centre, Sunway Medical Centre, KPJ Healthcare Berhad, Rehab and Physiotherapy Centre (such as Cerebral Palsy Children Association of Penang) and University Hospitals (such as Universiti Malaya Medical Centre; UMMC and Hospital Universiti Sains Malaysia, HUSM).[6-12]

There are several phenomenological classification of common gait disorders and **Figure 1** features a graphic representation of the step sequence in both normal gait and some key gait disorders.

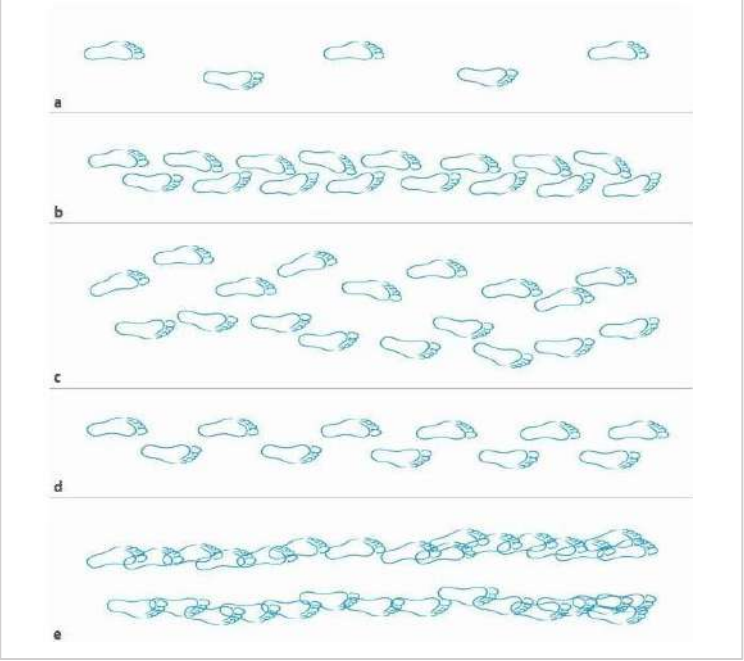


Figure 1: Graphic representation of the step sequence in classical gait disorders; a) normal gait, b) spastic paraparetic gait, c) cerebellar ataxic gait, d) parkinsonian gait and e) frontal

gait. Note narrow step width and inwards rotation in paraspastic gait, broadened base and marked irregularity in cerebellar gait, shortened and mildly irregular step length in parkinsonian gait and broad-based, short-stepped, irregular walking in frontal gait disorder.[13]

Neurological gait and balance impairments have been notoriously difficult to treat. For example, although some data suggests that freezing of gait in people with gait disorder may improve with levodopa, one study revealed that gait may worsen in treated patients possibly due to **drug**-induced dyskinesia.[14,15] As a result, there has been a shift towards non-pharmacological treatments. **Deep brain stimulation** has revolutionised the management of dopaminergic motor characteristics in many patients with severe Parkinson's disease. While there is some data supporting data brain stimulation in the treatment of gait abnormalities, it has had varying effects on the non-dopaminergic motor characteristics on gait and balance.[16] Meanwhile, non-invasive therapy methods such as **repeated transcranial magnetic stimulation** showed early promise in the treatment of gait, but subsequent trials utilising **intermittent magnetic stimulation** and **transcranial direct current stimulation** produced poor results.[17-20] **Physical therapy** remains the foundation of treatment for individuals with neurological gait and balance impairments, and it is known to generate long-term plastic changes in the cerebral cortex.[21-23]

For patients with gait disorders (such as stroke, spinal cord injury and multiple sclerosis), rehabilitation is the process of restoring or managing impaired functions.[24] A multidisciplinary team including physiotherapists, occupational therapists, speech therapists and neuropsychologists should provide integrated and holistic rehabilitation. Rehabilitation focuses on restoring motor skills through repetitive, high-intensity and task-specific activities. This process creates new neural connections that allow for the re-transmission of motor signals.[25] Over the years, various robotic systems have been utilised to rehabilitate patients through repetitive task-specific activities. Robotic assistive devices instruct patients' limbs to send and receive signals from the brain, leading to improved motor ability. These advanced systems, which include interactive automation, sensors and dynamic control logic can run with minimum involvement of physiotherapist participation.[26] Several devices have been used for rehabilitation of lower limb as shown in **Figure 2**.[27-29] The system is initially connected to the patient and physiotherapist will launch a software programme that simulates different stages of walking. The device will move the patient's lower limbs along with the physiotherapist controlling the tempo, guidance force and body weight support.[30]

(a) **(b)** **(c)** **(d)** **(e)**

Figure 2: a) Lokomat® by Hocoma, b) Gait Trainer™ by Reha-Stim Medtec, c) G-EO System™ by Reha Technology, d) Hybrid Assistive Leg® by Cyberdyne and e) ExoMotus M4 by Fourier Intelligence.[27-29]

Contrary to assisted robotic systems, conventional rehabilitation of the lower limbs without assistive devices requires at least two physiotherapists to instruct a patient to walk, which may result in inconsistent pace and pattern. Long-term exercise can be physically demanding for physiotherapists and hindering patient rehabilitation progress. Conventional physiotherapy is labor-intensive and can be challenging for physiotherapists. Providing an optimal rehabilitation programme can be time-consuming and costly for therapists and organisations.[31] On that account, robots enable physiotherapists to focus on functional rehabilitation during individual

training sessions and supervise numerous patients concurrently during robot-assisted therapy sessions. This technique is claimed to optimise the knowledge and time of physiotherapists, leading to more successful rehabilitation programmes.[27]

The current evidence base does not provide a clear determination of the effectiveness of robotic-assisted rehabilitation. This review was requested by Physiotherapy Unit of Hospital Sultanah Aminah, Johor Bahru to evaluate whether lower limb exoskeleton can be used as a practical rehabilitation therapy for patients with gait disorder.

2.0 OBJECTIVE/ AIM

The objective of this technology review was to assess the effectiveness, safety, organisational issue and economic implication of lower limb exoskeleton as a therapy option for patients with gait abnormality.

3.0 TECHNICAL FEATURES

According to Encyclopaedia of Biomedical Engineering (2019), robotic exoskeleton is defined as powered devices that attach around and to a human or animal body and contain actuators that deliver mechanical power to aid movement.[32] It is a complex system of interconnected components and **Figure 3**'s block diagram displays a typical collection of fundamental elements.[33] It operates via a system of biometric sensors actuated by nerve impulses delivered from the brain to various muscle groups, resulting in a precise motion. Electrical and computer patterns are utilised to create exoskeletons, allowing for the adaptability and production of movement in varying degrees.[34]

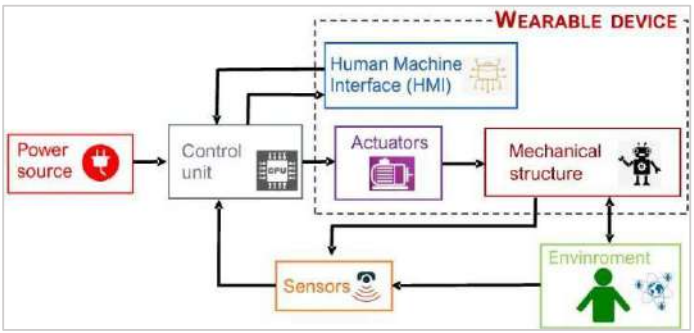


Figure 3: General design of a robotic exoskeleton. Actuators and sensors play critical roles in the exoskeleton system. Actuators are critical components of active devices, and the technologies used have a substantial impact on device performance. Sensors are required for interaction with the environment, particularly with the user of the exoskeleton. The options for actuator and sensor technology are frequently linked.[33]

The application fields of this technology have expanded to include healthcare (rehabilitation), construction, warehousing, material handling, manufacturing, sports and military. Given that the robot may reduce human physical effort while boosting mobility and movement speed, it is thought to have significant economic and ergonomic potential.[35]

In rehabilitation, robotic gait trainers provide repeated, rigorous and standardised gait training to patients, reducing the physical demands on therapists. Currently, multijoint aided lower limb training robots are divided into three generations. The first generation includes of weight-reducing exoskeleton robots that use hanging belts and sports running tables, such as the Lokomat. The second generation includes gait-assisted exoskeleton robots that can walk on

flat terrain, such as ReWalk, Ekso, HAL and Soft Exosuit. The third generation includes intelligent powered exoskeleton robots that incorporate technologies such as artificial intelligence, augmented reality, virtual reality and the Internet of Things, which provide assisted walking as well as additional capabilities such as FourierX2, UGO, BEAR-H1 and others. **Figure 4** is a typical representation of several generations of exoskeleton robots.

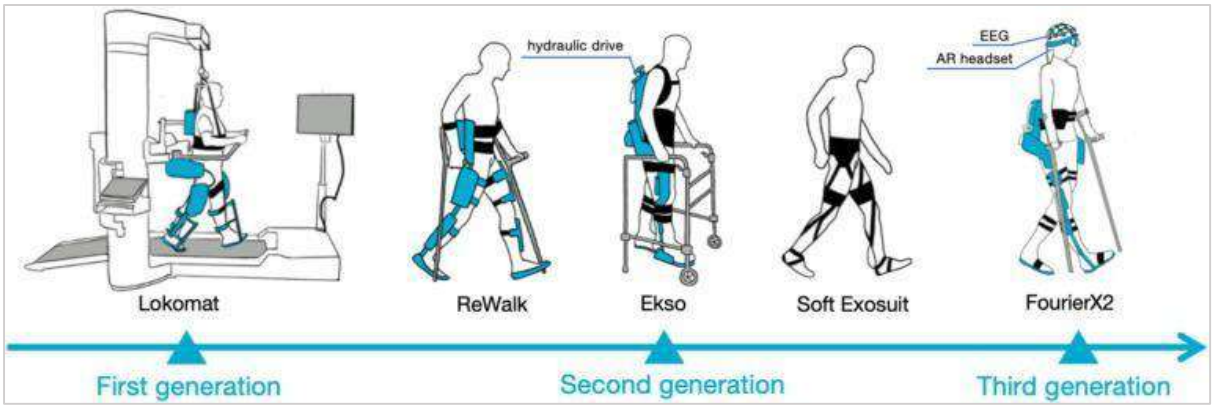


Figure 4: Various generations of exoskeleton robots for rehabilitation on gait.[36]

Patients also have access to a variety of motor feedback data, including leg and plantar loads, as well as joint motions with a special emphasis on the hip. The acquisition of motor feedback increases neurological healing and reduces problems via a variety of molecular processes **(see Figure 5)**.[36]

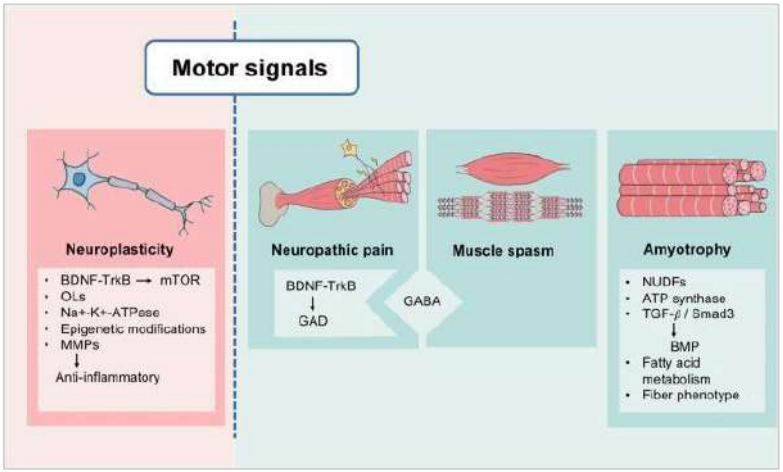


Figure 5: Molecular pathways connected with motor signals, revealing their involvement in encouraging neuroplasticity and alleviating difficulties.[36]

4.0 METHODS

The systematic review was conducted and search strategy was developed by the main author and reviewed by the co-author.

4.1 Searching

The following electronic databases were searched through the Ovid interface:

- Ovid MEDLINE® All <1946 to 12th July 2024>

Other databases: EMBASE, PubMed, Cochrane Library, US FDA, INAHTA

The specific search strategy employed are presented in **Appendix 1**. Additional articles retrieved from reviewing the bibliographies of retrieved articles. The search was limited to articles on human and until year 2014. There was no language limitation in the search and the last search was conducted on 12th July 2024.

4.2 Selection

A reviewer screened the titles and abstracts against the inclusion and exclusion criteria. The risk of bias for the included studies were assessed according to the criteria outlined in the ROBIS, Cochrane Risk of Bias (RoB 2.0) and CHEC-extended checklists. P-values less than 5.0% were considered as statistically significant. Studies were graded according to US/ Canadian Preventive Services Task Force **(Appendix 2)**. All data were extracted and summarised in evidence tables as in **Appendix 3**.

The inclusion and exclusion criteria were:

Inclusion criteria:

Population	Patients with gait disorder
Interventions	Lower limb exoskeleton
Comparators	Conventional rehabilitation therapy
Outcomes	**Effectiveness:** Improvement on gait assessment in related domains **Safety:** Adverse events related to treatment or device **Organisational:** Training, expertise **Economic implication:** Cost-effectiveness analysis, budget impact analysis
Study design	Health Technology Assessment reports, Systematic Review and Meta-Analysis, Randomised Control Trial, Non-randomised Control Trial, cohort studies, cross-sectional studies, case studies
Type of publication	Full text articles published in English

Exclusion criteria:

Study design	Animal studies, narrative reviews
Type of publication	Non-English full text articles

5.0 RESULTS

5.1 Selection of the included studies

The results of the study selection process are summarised in the PRISMA flow diagram in **Figure 6**. The initial searches yield a total of 9,085 citations from electronic database and 344 from Google Scholars, with 4,934 citations remaining following removal of duplicates. The titles of these citations were screened with a total of 239 titles deemed potentially relevant. The abstracts of those titles were examined and 228 full text articles were retrieved. Nineteen full articles were included after assessing for eligibility criteria, which consists of one systematic review and meta-analysis, three systematic reviews alone, 12 randomised controlled trials, two cost-effectiveness analysis studies and one budget impact analysis study. The studies were conducted mainly in United States, followed by countries in Asia Continents (Malaysia and South Korea), Europe Continents (Austria, Switzerland, Italy and United Kingdom) and Australia.

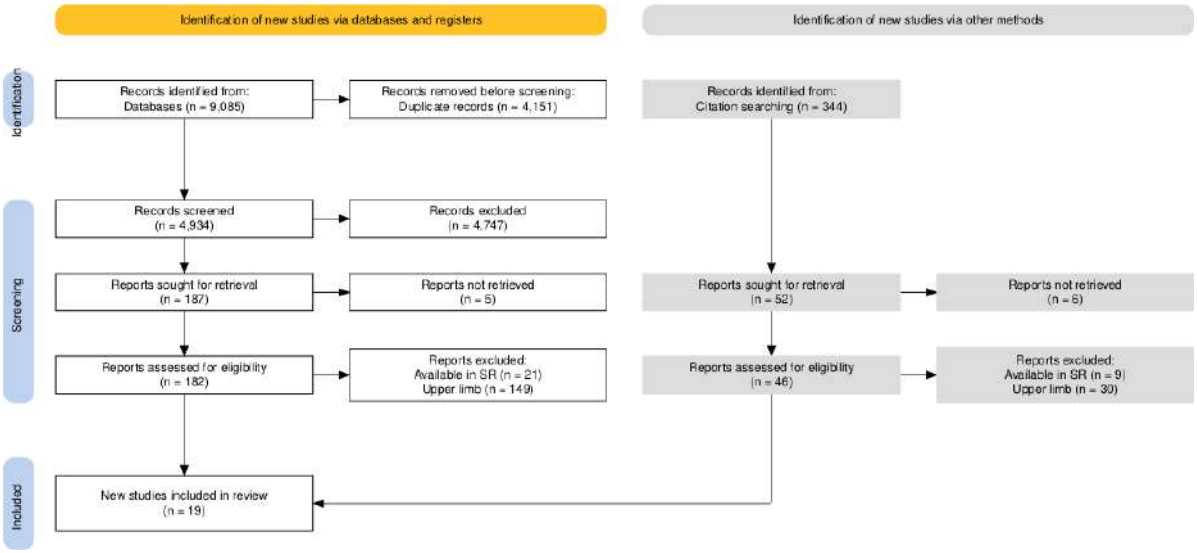


Figure 6: Flow chart of study selection for the search on lower limb exoskeleton for gait therapy (PRISMA Flow Diagram).[38]

5.2 Critical appraisal of the included studies

One reviewer systematically assessed the risk of bias of systematic reviews using ROBIS. One study in **Table 1** revealed high concerns regarding on specification of study eligibility criteria (there were no pre-defined objectives and eligibility criteria reported), methods used to identify and select studies (the author did not mention any appropriate range of database or electronic sources for published and unpublished reports), and methods used to collect data and appraise studies (no appraisal was done in all included reports).[39, level I]

Meanwhile, Cochrane RoB 2.0 checklist was utilised to assess the quality of randomised controlled trials **(Figure 7 and 8)**. Two studies showed high risk concerns due to bias arising on deviations of intended intervention; both studies applied the per-protocol effects (several patients did not adhere to the intervention completely due to different schedule protocols,[40, level I] and the number of patients decreased more in the intervention group as compared to control group[41, level I]). In addition, most of the studies demonstrated unclear concerns in selecting reported results; the majority of the numerical findings being evaluated were unlikely to have been chosen based on the outcomes of numerous eligible outcome measurements within the outcome domain, as well as multiple eligible data analyses.[40, 43-46, level I]

The CHEC-extended list was used to critically appraised the two cost-effectiveness analysis studies **(see Table 2)**. Both studies did not address the data' generalisability and transferability to different contexts and patient categories, and the costs were not valued appropriately (the year the cost was borne was not cited, no cost performance index was applied and the currency conversion was not undertaken to align costs with the study population where required).[47,48]

Table 1: Quality assessment of systematic review by using ROBIS.

	D1	D2	D3	D4	CONCLUSION
Yang FA et al./ 2022	+	+	+	+	+
Nurfarah Aqilah AN et al./ 2022	-	-	-	?	-
Goetz G et al./ 2020	+	+	+	?	+
Lo K et al./ 2017	+	+	+	+	+

		Judgement	
D1	Concerns regarding specification of study eligibility criteria	+	Low
D2	Concerns regarding methods used to identify and/or select studies	?	Unclear
D3	Concerns regarding methods used to collect data and appraise studies	-	High
D4	Concerns regarding the synthesis and findings		
CONCLUSION	Risk of bias in the review		

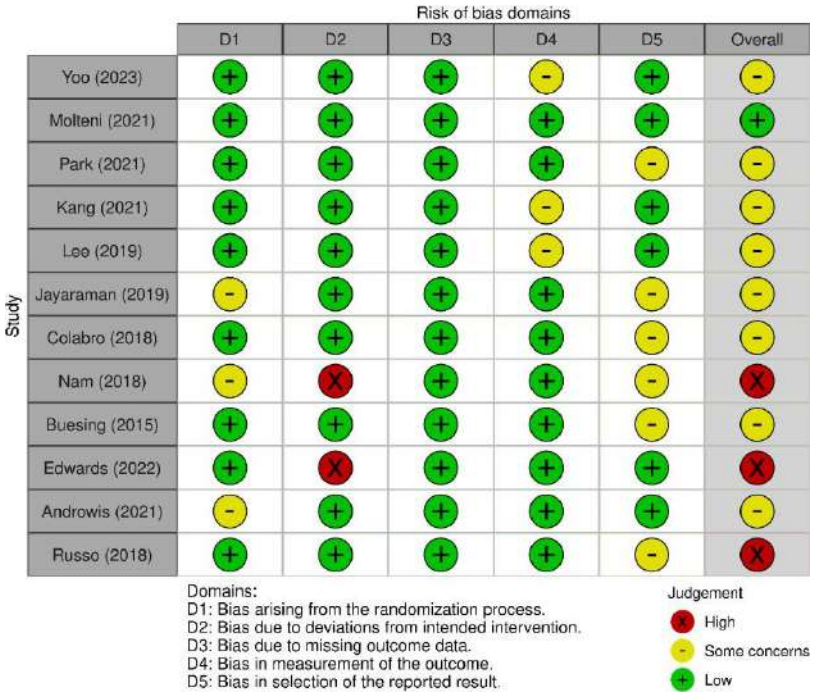


Figure 7: Quality assessment of randomised controlled trial by using Cochrane Risk of Bias 2.0 (traffic light plot).

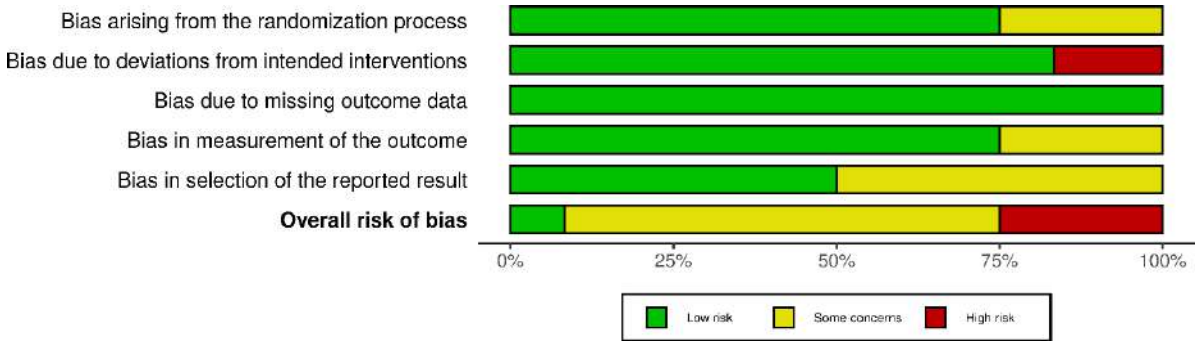


Figure 8: Quality assessment of 12 randomised controlled trials by using Cochrane Risk of Bias 2.0 (summary plot).

Table 2: Quality assessment of cost-effectiveness analysis studies by using CHEC-extended.

Question	Checklist	Decision	
		Pinto D et al./ 2023	Manetti S et al./ 2020
1	Is the study population clearly described?	Y	Y
2	Are competing alternatives clearly described?	Y	N
3	Is a well-defined research question posed in answerable form?	Y	N
4	Is the economic study design appropriate to the stated objective?	Y	Y
5	Are the structural assumptions and the validation methods of the model properly reported?	N	Y
6	Is the chosen time horizon appropriate in order to include relevant costs and consequences?	Y	U
7	Is the actual perspective chosen appropriate?	Y	Y
8	Are all important and relevant costs for each alternative identified?	Y	Y
9	Are all costs measured appropriately in physical units?	Y	Y
10	Are costs valued appropriately?	N	N
11	Are all important and relevant outcomes for each alternative identified?	Y	Y
12	Are all outcomes measured appropriately?	Y	Y
13	Are outcomes valued appropriately?	Y	Y
14	Is an appropriate incremental analysis of costs and outcomes of alternatives performed?	Y	Y
15	Are all future costs and outcomes discounted appropriately?	N	Y
16	Are all important variables, whose values are uncertain, appropriately subjected to sensitivity analysis?	N	Y
17	Do the conclusions follow from the data reported?	Y	N
18	Does the study discuss the generalisability of the results to other settings and patient/client groups?	N	N
19	Does the article/report indicate that there is no potential conflict of interest of study researcher(s) and funder(s)?	Y	Y
20	Are ethical and distributional issues discussed appropriately?	N	Y
	Total Yes	14	14
	Total No	6	5
	Total Unclear	0	1
	Total Percentage of Yes	**70**	**70**

5.3 Effectiveness of lower limb exoskeleton

Seven studies enrolled stroke,[40,43,49,51-54, level I] two study enrolled patients with spinal cord injury[41, level I] and further two studies enrolled patients with multiple sclerosis.[46,56 level I]

a. Stroke

A horizon screening review of early evidence regarding lower limb exoskeleton for stroke was undertaken by Nurfarah Aqilah AN et al. (2022). A total of four studies comparing soft exoskeleton therapy with no intervention was included. Maximum walking speed (1:0.30 m/s) and 6MWT (1:59m) were shown to improve significantly. At a comfortable and maximal walking pace, there were significant improvements in paretic peak propulsion (1:2.80%BW; 1:4.63%BW) and trailing limb angle (1:6.2°; 1:4.30°) ($p<0.05$). Furthermore, four out of seven patients (57.1%) improved their ability to climb and descend ≥5 stairs with help, as well as develop outdoor walking abilities.[39, level I]

Seventeen studies were included in the systematic review by Goetz G et al. (2020), to evaluate the potential clinical benefit of robotic assisted rehabilitation with regard to functional outcomes in stroke patients. The study included inpatient, rehabilitative and outpatient care to compare the robotic-assisted rehabilitation with standard gait rehabilitation. It reported on the effectiveness of three types of exoskeletons as follows:[49, level I]

i. Stationary exoskeletons

   Overall, there was moderate quality evidence that robotic-assisted intervention did not enhance ability to walk and balance when compared to conventional physiotherapy. The low quality findings also showed that it might not enhance walking speed or gait distance as compared to physiotherapy-assisted locomotion training.

ii. Portable exoskeletons: double-leg and single-leg exoskeletons

   Overall, there was no evidence that training using a portable exoskeleton and weight bearing improved walking ability, gait distance and balance more than conventional gait training.

iii. Stationary end-effectors

   Ability to walk was reported in four studies (subacute and chronic stroke; n=331). While two studies demonstrated a significant between-group difference in favour of end-effector-based gait training in the subacute phase, the remaining studies found no significant difference between end-effector-assisted and conventional gait training.

   Walking speed was measured in five studies (subacute and chronic stroke; n=361). While two trials demonstrated a statistically significant difference between groups in favour of end-effector aided gait training, the remaining three studies did not find a meaningful difference.

   Four studies (subacute and chronic stroke; n=331) reported gait distance. Only one of these studies demonstrated a statistically significant between-group difference in favour of end-effector-based gait training.

   Balance was reported in two studies (subacute and chronic stroke; n=146). Neither study found a statistically significant difference between groups preferring end-effector-based gait training.

Lo K et al. (2017) conducted a meta-analysis to examine the effectiveness of robotic devices in the rehabilitation of stroke patients for lower limb mobility and activities of daily living (ADL). The sustainability of treatment effect was also examined for more than three months in 51 studies (701 patients; age ≥18 years old). For walking test in the subgroup analysis for acute/ subacute, chronic and moderate/ mild impairment patients, there were no significant differences between experimental and control groups [acute/ sub-acute: p=0.23); chronic: p=0.59); moderate/mild: p=0.29)]. However, for severe impairment patients, a statistically significant difference favoring the experimental group was found. The pooled standardised mean difference (SMD) of random-effects model in **Figure 9** was 0.41 (95% CI 0.19 to 0.63, I^2=28.0%, p=0.0003).[50, level I]

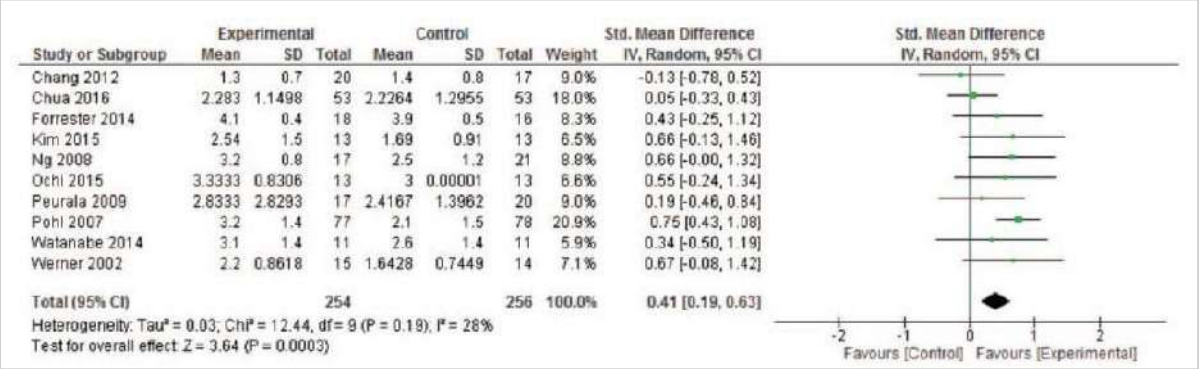


Figure 9: Effect of robotic therapy in experimental group compared with conventional therapy control group on lower limb walking (severe impairment).[50, level I]
SD, standard deviation; CI, confidence interval

Yoo HJ et al. (2023) in a randomised controlled trial, investigated the efficacy and practicality of 12 sessions of overground robot-assisted gait training in subacute stroke patients from January 2020 to June 2021. Seventeen subacute stroke survivors (age ≥ 18 years old) from Department of Rehabilitation Medicine of Korea University Anam Hospital were enrolled. All patients went through a standard daily stroke neurorehabilitation programme (90 minutes per day, five days per week, for four weeks), which comprised physical and occupational therapy. In the intervention group (n=9), the overground robot-assisted gait training was used in adjunct with the conventional training, whereas conventional manual gait training was provided by a physiotherapist to the control group (n=8). The exoskeleton group had higher median values for motor function, balance, walking test and ADL compared to the control group, but the difference was not statistically significant. In contrast, the exoskeleton group had a substantially higher EQ-5D score (0.767 versus 0.434 in the control group, p=0.028); ((EQ-5D: the scores from the descriptive component can be reported as a five digits number ranging from 11111 [full health] to 55555 [worst health)]) and FAC score (p<0.05); (functional walking test that evaluates ambulation ability, 0 indicates non-functional ambulatory, 5 indicates independent ambulator who can walk freely on any suface)). In terms of patient satisfaction, patients were particularly satisfied with the safety, comfort and effectiveness domains (median 4.5, range 3 to 5). On the other hand, several patients experienced pain in the weight, adjustments and durability domains, with a score of 2 indicating dissatisfaction. No participant reported difficulties or discomfort with the study protocol.[51, level I]

Another randomised controlled trial by Molteni F et al. (2021) also reported the mutual study objective and protocols as Yoo HJ et al. (2023).[51, level I] However, this study recruited higher number of patients (n=75) from March 2016 to April 2019 in five different Italian rehabilitation hospitals. The findings showed significant improvement in both groups in terms of gait distance, muscle strength, balance and ADL (p<0.0001) when compared to baseline. The questionnaire on the patients' usability and acceptability of the intervention was analysed. The

results revealed that the patients considered the robotic therapy positively. It was rated as comfortable (5.78±1.81), pleasant (5.91±1.5), somewhat painful (1.09±2.09) and demanding (2.96±2.10). The patients also found the robotic therapy valuable (6.22±1.13), would recommend it (6.35±1.07) and want to utilise it further in the near future (5.57±2.23).[52, level I]

Park C et al. (2021) enrolled 20 patients with acute hemiparetic stroke (mean age 73.0±12.72 years; 12 females, 8 males; age ≥ 18 years old), from Burke rehabilitation hospital, New York into a randomised controlled trial. This study compared the effects of the combination of both exoskeleton and conventional physical therapy, with the combination of conventional physical therapy and gait training. The paired t-test revealed that, in exoskeleton group showed substantially improvements in knee joint angle (M=26.69, SD=1.10; p=0.00; demonstrating better knee joint mobility), hip active force (M=1.32, SD=0.52; p=0.03), knee active force (M=1.66, SD=1.95; p=0.04) and ankle active force (M=1.52, SD=1.06; p=0.02), suggesting an improved coordinated force between the hip, knee and ankle joints.[42, level I]

Apart from that, there were also significant increase in the hip resistive force (M=2.08, SD=0.11; p=0.00), knee resistive force (M=0.12, SD=0.09; p=0.001) and ankle resistive force (M=−0.07, SD=0.53; p=0.001). In the perspective of joint stiffness in exoskeleton group, all data reported significant improvements in hip stiffness (M=0.72, SD=0.17; p=0.00), knee stiffness (M=0.72, SD=0.17; p=0.00) and ankle stiffness (M=0.40, SD=0.11; p=0.04).[42, level I]

The ANOVA revealed significant changes in the hip extensor and ankle dorsiflexor Modified Ashworth Scale (MAS) scores (to measure the increase of muscle tone) between the both groups (p=0.000; 0.043). The post-hoc analysis indicated that exoskeleton group resulted in more decreased hip extensor and ankle dorsiflexor spasticity than control group, suggesting that patients with hemiparetic stroke experienced decreased muscle spasticity after the intervention only.[42, level I]

A randomised controlled trial conducted by Lee HJ et al. (2019), investigated the effects of gait training with exoskeleton on locomotor function in 26 chronic stroke patients (age > 20 years old). The training intervention lasted four weeks and consisted of three sessions each week. All patients performed a gait training programme consisting of ten sessions: five treadmill sessions and five over-ground gait training sessions with wearable hip-assisted robot in the intervention group. After 10 training sessions, the intervention group showed significant improvement in FMA scale-lower limb (to assess motor function) and K-FES (fall assessment) compared to the control group (p<0.05). Moreover, spatiotemporal gait metrics such as gait speed, cadence and stride length increased significantly in both groups. Significant group-time interactions were seen for all spatiotemporal gait measures, with the experimental group showing better improvement than the control group (p<0.05).[53, level I]

In addition, gait training substantially enhanced muscular efforts (percentage of maximum voluntary contraction) on the afflicted side during the gait cycle compared to the control group. Positive results were seen in all gait symmetry ratios, including temporal step symmetry by 27.88%, spatial step symmetry by 32.97% and a decrease in muscle effort symmetries in rectus femoris (45.15%), biceps femoris (48.16%), tibialis anterior (34.20%) and gastrocnemius (34.62%) in the experimental group (p<0.05). Meanwhile, the control group only showed an improvement in rectus femoris muscle effort symmetry (27.41%; p<0.05).[53, level I]

There was another randomised controlled trial investigated walking exoskeleton robot's effects in 30 patients with chronic stroke, age ≥ 18 years old, which was undertaken by Kang CJ et al. (2021). The study was enrolled from November 2018 to May 2019 in a tertiary hospital, Asan Medical Center, South Korea. The conventional physiotherapy (n=15) relied on standard neurodevelopmental treatment procedures; patients worked on passive and active range of motion exercises, strengthening exercises, sitting and standing balance, sit-to-stand mobility,

and functional gait training. After treatments, the intervention group's muscle spasticity and step length improved significantly. Albeit the control group showed significant increases in balance, muscle spasticity and stride length, the intervention group however outperformed the control group in terms of step length of the afflicted leg, then again the differences were not statistically significant. From the patients' perspective in terms of satisfaction, the self-questionnaire in the intervention group revealed a treatment satisfaction rating of 3.6 out of 4.0 points.[54, level I]

Jayaraman A et al. (2019) in another randomised controlled trial, hypothesised that gait training with hip-assistive robotic exoskeleton improves clinical outcomes and strengthens the descending corticospinal drive to the lower limb muscles in patients with chronic stroke. Fifty patients (age 18 to 85 years old) were recruited between November 2013 and November 2014 from the Shirley Ryan AbilityLab and two satellite clinics in United States. The intervention (n=25) comprised of therapist-guided gait training with exoskeleton for 45 minutes per session, three times per week for six to eight weeks (18 sessions total), meanwhile the control group (n=25) underwent intensity-matched functional gait training. At the middle duration of the study, the intervention group showed improvement in functional gait (mean 22.6 [SD 37.4]), balance confidence (mean 5.2 [SD 5.2]) and fall efficacy (mean 8.2 [13.5]) compared to baseline, which was not evident in control group. In addition, there were significant effects of intervention on percentage change in gait distance in the 6MWT (p=0.030) and balance in the Berg Balance Scale (BBS; p=0.036), with the intervention group outperforming the control group.[43, level I]

In haemorrhagic stroke patients, balance improved substantially in the intervention group as compared to control group (p=0.029). On top of that, BBS scores increased by 24.7% (20.1) and 6.1% (4.0) in the intervention group for haemorrhagic and ischemic subtypes, respectively compared to 6.8% (6.7) and 7.7% (7.3) in control group. In terms of steps number, the average (SD) daily step count on therapy days was higher in the intervention group 4,366 (2,426) steps versus 3,028 (1,510) steps for the control group (p=0.013). In comparison to their average step count on non-treatment days, patients raised their step count on therapy days by 88.0% (82.4) in intervention group and 61.4% (43.5) in control group.[43, level I]

Most of the stroke-related studies included patients from age of 18 years. Meanwhile in a randomised controlled study by Calabro RS et al. (2018) selected 40 eligible patients (age ≥ 55 years old) from Neurorobotic Rehabilitation Unit in Italy, between May and August 2017. Both groups received conventional physiotherapy training (including a 15-minute warm-up and cool-down phase), which was scheduled five times per week for eight weeks. In addition to conventional training, the experimental group (n=20) received 45 minutes of exoskeleton gait training for eight weeks. Specifically, the results showed several significant improvements in the experimental group as compared to control group:[44, level I]

- Gait quality index : $F_{(1,38)}=43$, $p<0.001$, $d=0.9$
- Step cadence : $F_{(1,38)}=17$, $p<0.001$, $d=0.9$
- Gait cycle duration (affected limb) : $F_{(1,38)}=17$, $p<0.001$, $d=0.9$
- Stance/ swing ratio (affected limb) : $F_{(1,38)}=8.6$, $p=0.008$, $d=0.8$
- Gait cycle duration (unaffected limb) : $F_{(1,38)}=12$, $p<0.001$, $d=0.9$
- Stance/ swing ratio (unaffected limb) : $F_{(1,38)}=14$, $p<0.001$, $d=0.9$

Additionally, the electromyography amplitude of paretic muscles during the whole gait cycle at the end of training were impacted more in the experimental group ($F_{(3,57)}=4.3$, $p=0.007$, d 0.8) than in control group ($F_{(3,57)}=2.8$, $p=0.04$, $d=0.6$), as compared to the non-paretic. From the motor function aspects, the exoskeleton intervention caused a rebalancing of the sensory-motor integration of the affected and unaffected hemispheres, similar to corticospinal

excitability interhemispheric re-modulation, whereas the control group had a greater effect on the affected hemisphere only.[44, level I]

The relationship of electromechanical exoskeleton gait training on ambulatory function was assessed by Nam YG et al. (2018) in another randomised controlled trial in 40 stroke patients (age > 19 years old), from October to December 2016 in South Korea. The intervention group (n=18) performed electromechanical-assisted gait training as an adjunct with conventional physical therapy, meanwhile the control group continued for conventional physical therapy consisted of joint range-of-motion exercise, muscle strengthening and sit-to-stand (vice versa). Despite showing significant improvements of FAC in both groups (intervention: 0.64±0.16; control: 0.20±0.17), the data reported that there was no statistically significant difference between them.[40, level I]

Fifty chronic stroke patients (age 18 to 85 years old; 33 males and 17 females) were recruited in a randomised controlled trial, which was conducted by Buesing C et al. (2015) in the United States. The study compared the effects of wearable exoskeleton (n=25) with functional task specific training (n=25) on spatiotemporal gait parameters. By comparing with the baseline, the exoskeleton group showed various significant data ($p<0.008$):[45, level I]

- Walking speed velocity improved significantly at mid- and post-test.
- Cadence increased significantly at mid-, post- and follow-up testing.
- Stance time decreased significantly at mid-, post- and follow-up testing on both the impaired and non-impaired sides.
- Swing time decreased significantly on the impaired side at mid-, post- and follow-up tests.
- Step length increased significantly at mid-, post- and follow-up tests on the impaired side.
- The stride length increased significantly at mid-, post- and follow-up tests on both the impaired and non-impaired sides.
- Temporal asymmetry decreased significantly at post-test.

b. Spinal cord injury (SCI)

Yang FA et al. (2022) successfully conducted a systematic review and meta-analysis to assess the effect of training protocol related to three different regimes of interventions; body weight-supported overground training, body weight-supported treadmill training and robot-assisted gait training. The data of 497 patients in 15 included studies were obtained from several electronic databases (PubMed, Cochrane Library, Scopus and Embase) from August 2022 onwards. **Figure 10** depicts a network diagram of the integrated body weight-supported gait training regimens. Each treatment has at least one placebo-controlled study. The pooled SMDs of functional scores in the network meta-analysis indicated that robot-assisted gait training was significantly more beneficial than the control intervention. The comparisons between the control group and additional body weight-supported gait training regimes showed robot-assisted gait training outperformed the other two regimes: robot-assisted gait training = 0.30 (0.11 to 0.50), body weight-supported treadmill training = 0.09 (− 0.40 to 0.58) and body weight-supported overground training = 0.09 (− 0.55 to 0.73). Meanwhile **Figure 11 and 12** demonstrates that robot-assisted gait training dominated control intervention significantly in the ambulatory assessment.[55, level I]

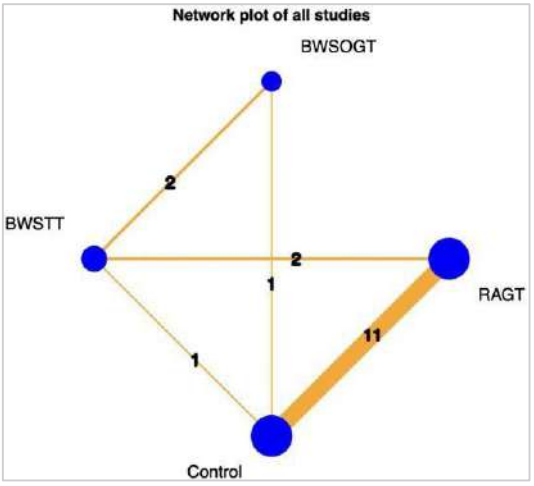


Figure 10: Network plot of all studies. The nodes, which represent the interventions in the network and the lines, which highlight the available direct comparisons between pairs of interventions. The size of the nodes and the width of the lines both represent the number of studies.[55, level I]

RAGT, robot-assisted gait training; BWSTT, body weight-supported treadmill training; BWSOGT, body weight-supported overground training

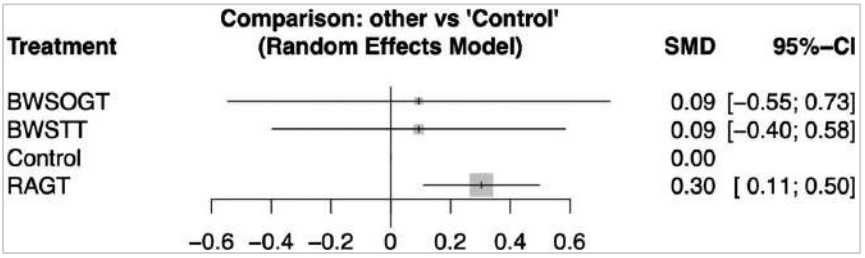


Figure 11: Forest plot of ambulatory assessments. The SMDs and 95% CIs of comparison between the control intervention and other body weight-supported gait training therapies were as follows: RAGT = 0.30 (0.11, 0.50); BWSTT = 0.09 (− 0.40, 0.58); and BWSOGT = 0.09 (− 0.55, 0.73).[55, level I]

RAGT, robot-assisted gait training; BWSTT, body weight-supported treadmill training; BWSOGT, body weight-supported overground training; SMD, standardised mean difference; 95% CI, 95% credible interval

Furthermore, the distribution of probabilities in the ranking of each training approach was investigated. The ranking probabilities showed that, robot-assisted gait training was the most successful, followed by body weight-supported overground training, body weight-supported treadmill training and the control intervention **(see Figure 13)**.[55, level I]

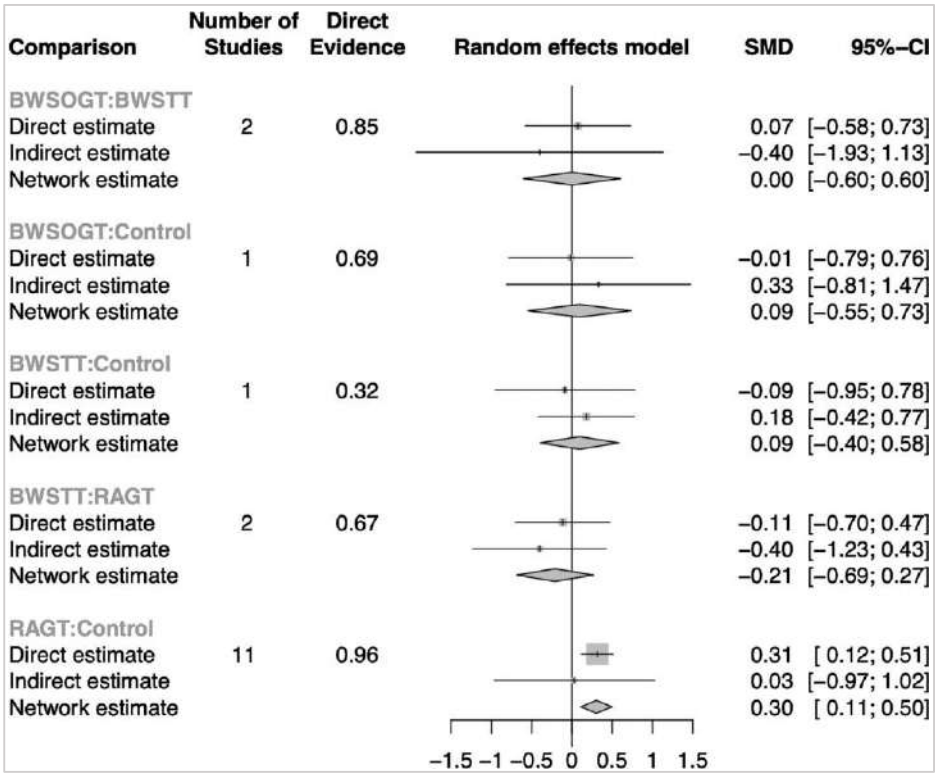


Figure 12: Forest plots of pairwise meta-analyses and network meta-analyses of ambulatory assessments.[55, level I]

RAGT, robot-assisted gait training; BWSTT, body weight-supported treadmill training; BWSOGT, body weight supported overground training

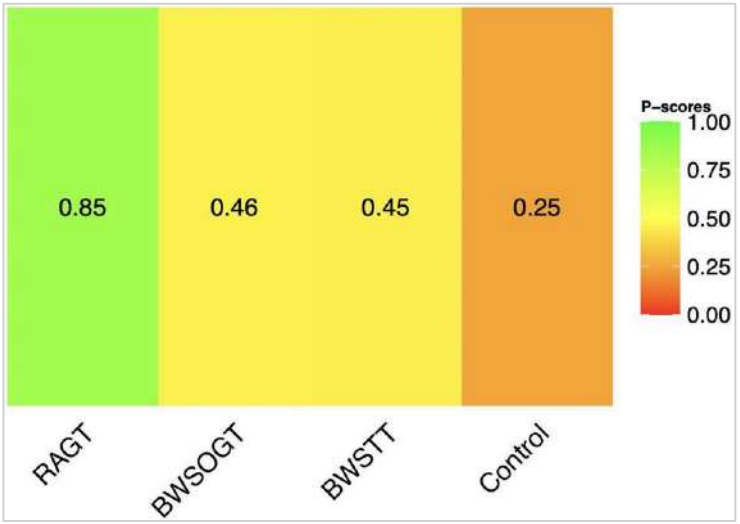


Figure 13: Distribution of probabilities in the ranking of each body weight-supported gait training strategy.[55, level I]

RAGT, robot-assisted gait training; BWSTT, body weight-supported treadmill training; BWSOGT, body weight–supported overground training

In a randomised controlled trial conducted by Edwards DJ et al. (2022), 33 patients with chronic incomplete SCI were recruited between September 2016 to September 2019 across seven sites in United States. Patients in the intervention group (n=14) were required to complete the training regimen as run-in participants to ensure that assessment and training procedures were practiced and followed in accordance with the clinical trial protocol. Two

different control groups conducted different training regimes; a) active control group (n=13) comprised of 45-minute of body weight-supported treadmill training and if possible, overground training without body weight support, b) passive control group (n=6) continued with daily activities as normal. After the 12-week intervention, the exoskeleton group had shown a 51.0% increase in self-selected gait speed (mean SD 0.18±0.23 m/s), followed by other two control groups; active control increased by 32.0% (0.07±0.11 m/s) and passive control by 14.0% (0.03±0.03 m/s), with no significant differences between groups (p>0.05).[41, level I]

Aside from that, the median distance covered in the 6MWT following the 12-week intervention was the highest in the intervention group, 538.0 feet (quartile 268.0 to 687.3), followed by 346.6 feet (quartile 219.5 to 711.5) for the active control and 320.0 feet (quartile 148.8 to 466.6) for the passive control, representing improvements of 34.0%, 28.0% and 18.0%, respectively. Similarly, the intervention group reported the shortest median time for timed-up-and-go, 26.4 s (quartile 17.3 to 53.0), followed by 30.0 s (quartile 26.0 to 70.7) for active control and 46.0 s (quartile 29.0 to 64.9) for the passive control, thus representing improvements of 18.7%, 19.9%, and 12.7% respectively with no significant differences between groups (p>0.05).[41, level I]

c. Multiple sclerosis

Androwis GJ et al. (2021) conducted a randomised controlled trial to study the effects of 4-week of robotic exoskeleton on functional mobility, walking endurance, cognitive processing speed and thalamocortical resting-state functional connectivity in 10 patients with multiple sclerosis. The patients (age 18 to 75 years old) were recruited directly from the Kessler Institute for Rehabilitation in United States. The experimental training (n=6) involved supervised and progressive walking training overground in the robotic exoskeleton and led by a licensed physiotherapist, meanwhile the control training (n=4) comprised of conventional gait training. The evidence showed substantial improvements of timed-up-and-go performance (d=-1.20) and 6MWT (d=0.80) in robotic exoskeleton group relative to minimal change in the control group. In terms of motor and thalamocortical functions, the patients underwent robotic exoskeleton training demonstrated substantial improvements in SDMT (9.2 points; represents the core neuropsychological domain of processing speed) and thalamocortical resting-state functional connectivity relative to substantial worsening for those who underwent conventional gait training (4.5 points) (SDMT performance, d=1.42; thalamocortical resting-state functional connectivity, d=1.64, see **Figure 14**).[56, level I]

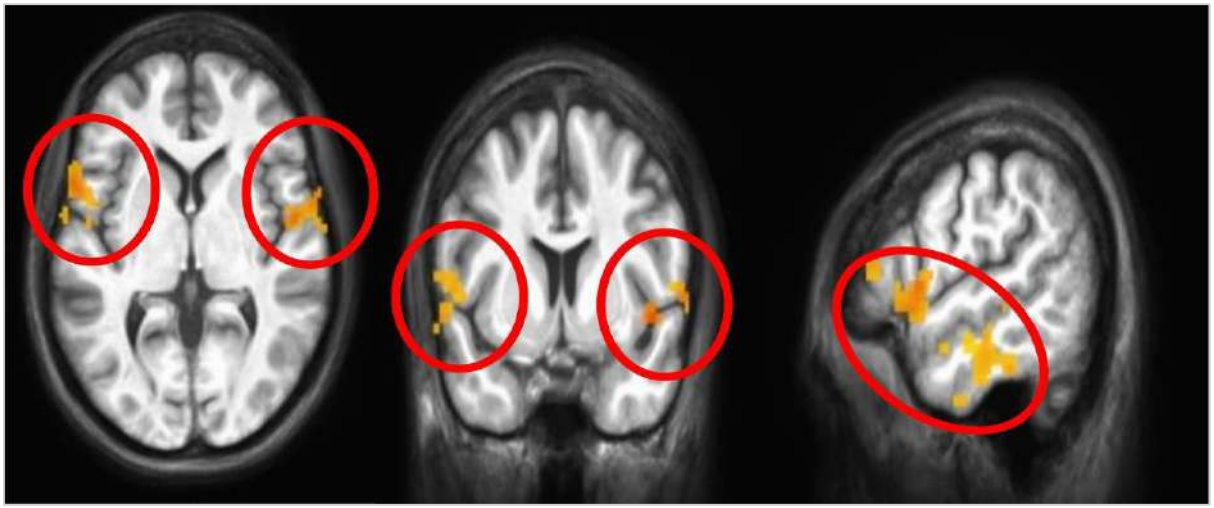


Figure 14: Increases in resting-state functional connectivity between the thalamus and ventromedial prefrontal cortex for persons with multiple sclerosis who underwent robotic exoskeleton training relative to those who underwent conventional gait training thalamocortical resting-state functional connectivity.[56, level I]

Another randomised controlled trial on multiple sclerosis was conducted by Russo M et al. (2018) to investigate whether an intensive robotic gait training, preceding a traditional rehabilitative treatment could be useful in improving and potentiating motor performance in 45 patients (mean SD age: 42±7 years; 66.6% females). The experimental group (n=30) had a 6-week robotic training prior to 12 weeks of traditional training, whereas the control group received 18 weeks of conventional rehabilitation training that included general conditioning activities. From baseline to six weeks of the study, the experimental group exhibited substantial improvement ($p<0.001$) in FIM (to assess a patient's level of disability), TBS (the lower the score on the TBS test, the higher the risk of falling) and timed-up-and-go, while control group only improved in timed-up-and-go ($p<0.001$). In contrast, from six weeks to at the end of the rehabilitative training, the experimental group had an improvement only regarding timed-up-and-go ($p<0.001$). A significant worsening in timed-up-and-go was observed in the experimental group one month after the end of the training ($p<0.01$).[46, level I]

Above all, the effectiveness of lower limb exoskeleton on gait therapy are summarised in **Table 3**.

Table 3: A summary of effectiveness of lower limb exoskeleton for gait therapy.

Study	Patient characteristic	Follow up duration	Intervention		Findings
			Treatment	Control	
Patients with stroke					
Nurfarah Aqilah AN et al. 2022 Horizon Scanning[39]	4 studies consisted of 1 SR, 1 RCT, 1 clinical trial, 1 concept study	NI	Soft exoskeleton	No exoskeleton and no comparator	• Soft exoskeleton improved clinically and significantly on maximum walking speed (1:0.30 m/s) and 6MWT (1:59m). • Significant improvements in paretic peak propulsion, propulsive power and trailing limb angle ($p<0.05$) for walking pace. • Paretic peak propulsion and trailing limb angle improved significantly ($p<0.05$) for walking speed. • 4/7 patients (57.1%) improved their ability to climb and descend ≥5 stairs with help, as well as develop outdoor walking abilities.
Goetz G et al. 2020 SR[49]	17 studies consisted of 1 Cochrane review and 16 primary studies	NI	Robotic-assisted rehabilitation	Standard gait rehabilitation	• Five studies demonstrated a significant between-group difference in favor of end-effector-based gait training for walking ability, walking speed and gait distance.
Lo K et al. 2017 SR and MA[50]	15 studies 701 patients Age > 18 years Acute/ subacute, chronic, moderate/ mild impairments	After 3 months	Robotic-assisted rehabilitation	Standard gait training	• For walking test in severe impairment patients, a statistically significant difference favoring the experimental group; pooled SMD (random-effects model) was 0.41 (95% CI 0.19 to 0.63, I^2=28.0%, p=0.0003).
Yoo HJ et al. 2023 RCT[51]	17 patients Age ≥ 18 years Subacute stroke	NI	Overground robot-assisted gait training + conventional training	Conventional training	• The exoskeleton group had a substantially higher EQ-5D score (0.767 versus 0.434 in the control group, p=0.028) and FAC score ($p<0.05$). • Patients satisfied with the safety, comfort and effectiveness domains (median 4.5, range 3 to 5).
Molteni F et al. 2021 RCT[52]	75 patients Subacute stroke	NI	Wearable powered exoskeleton + conventional training	Conventional training	• Both groups showed significant improvement in in terms of gait distance, muscle strength, balance and ADL ($p<0.0001$) when compared to baseline. • The patients' usability and acceptability were rated as comfortable (5.78±1.81), pleasant (5.91±1.5), somewhat painful (1.09±2.09), demanding (2.96±2.10), valuable (6.22±1.13), would recommend it (6.35±1.07) and want to utilise it further in the near future (5.57±2.23).
Park C et al. 2021 RCT[42]	20 patients Age ≥ 18 years Acute hemiparetic stroke	NI	Hip interlimb coordinated humanoid robot + conventional physical therapy	Conventional physical therapy + gait training	• Exoskeleton group showed substantially improvements in knee joint angle (M=26.69, SD=1.10; p=0.00), hip active force (M=1.32, SD=0.52; p=0.03), knee active force (M=1.66, SD=1.95; p=0.04) and ankle active force (M=1.52, SD=1.06; p=0.02). • Exoskeleton group showed significant increase in the hip resistive force (M=2.08, SD=0.11; p=0.00), knee resistive force (M=0.12, SD=0.09; p=0.001) and ankle resistive force (M=−0.07, SD=0.53; p=0.001), hip stiffness (M=0.72, SD=0.17; p=0.00), knee stiffness (M=0.72, SD=0.17; p=0.00) and ankle stiffness (M=0.40, SD=0.11; p=0.04). • There were significant changes in the hip extensor and ankle dorsiflexor MAS scores between the both groups (p=0.000; 0.043).
Lee HJ et al. 2019 RCT[53]	26 patients Age > 20 years Chronic stroke	NI	Wearable hip-assisted robot + standard gait training	Standard gait training	• Exoskeleton group showed significant improvement in FMA scale-lower limb and K-FES compared to the control group ($p<0.05$). • Exoskeleton group reported better improvement in all spatiotemporal measures than the control group ($p<0.05$). • Positive results were seen in all gait symmetry ratios in exoskeleton group ($p<0.05$).

Kang CJ et al. 2021 RCT[54]	30 patients Age ≥ 18 years Chronic stroke	NI	Walking exoskeleton robot training	Standard neuro-developmental treatment	• Exoskeleton group's muscle spasticity and step length improved significantly. • The self-questionnaire in the exoskeleton group revealed a treatment satisfaction rating of 3.6 out of 4.0 points.
Jayaraman A et al. 2019 RCT[43]	50 patients Age 18 to 85 years Chronic stroke	3 months	Therapist-guided gait training with exoskeleton	Intensity-matched functional gait training	• Exoskeleton group showed improvement in functional gait (mean 22.6 [SD 37.4]), balance confidence (mean 5.2 [SD 5.2]) and fall efficacy (mean 8.2 [13.5]). • There were significant effects on percentage change in gait distance in the 6MWT (p=0.030) and balance in the BBS (p=0.036). • In haemorrhagic stroke patients, balance improved substantially in the intervention group (p=0.029), BBS scores increased by 24.7% (20.1) compared to 6.8% (6.7) in control group. • The average (SD) daily step count on therapy days was higher in the intervention group 4,366 (2,426) steps versus 3,028 (1,510) steps for the control group (p=0.013).
Calabro RS et al. 2018 RCT[44]	40 patients Age ≥ 55 years	NI	Exoskeleton gait training + conventional physiotherapy training	Conventional physiotherapy training	• Exoskeleton groups showed significant results as compared to control group in gait quality index, step cadence, gait cycle duration in both limbs and stance/ swing ratio in both limbs. • The electromyography amplitude of paretic muscles during the whole gait cycle at the end of training were impacted more in the exoskeleton group ($F_{(3,57)}$=4.3, p=0.007, d 0.8) than in control group ($F_{(3,57)}$=2.8, p=0.04, d=0.6).
Nam YG et al. 2018 RCT[40]	40 patients Age > 19 years	NI	Electromechanical-assisted gait training + conventional physical therapy	Conventional physical therapy	• There were significant improvements of FAC in both groups (intervention: 0.64±0.16; control: 0.20±0.17).
Buesing C et al. 2015 RCT[45]	50 patients Age 18 to 85 years Chronic stroke	3 months	Wearable exoskeleton	Functional task specific training	• Exoskeleton group showed significant improvement in walking speed, cadence, stance time, swing time, step length, stride length and temporal asymmetry as compared to baseline (p<0.008).
Patients with spinal cord injury					
Yang FA et al. 2022 SR and MA[55]	15 studies 497 patients	NI	Robot-assisted gait training, Weight supported overground training, Weight-supported treadmill training	Placebo	• Robot-assisted gait training dominated control intervention significantly in the ambulatory assessment. • The ranking probabilities showed that, robot-assisted gait training was the most successful, followed by body weight-supported overground training, body weight-supported treadmill training and the control intervention.
Edwards DJ et al. 2022 RCT[41]	33 patients Chronic incomplete spinal cord injury	NI	Exoskeleton gait training	Standard gait training, No training	• Exoskeleton group had shown the highest increase (51.0%) in self-selected gait speed (mean SD 0.18±0.23 m/s) and mean distance covered in the 6MWT, 538.0 feet (quartile 268.0 to 687.3; 34.0% improvement). • Exoskeleton group reported the shortest median time for timed-up-and-go, 26.4 s (quartile 17.3 to 53.0).
Patients with multiple sclerosis					
Androwis GJ et al. 2021 RCT[56]	10 patients Age 18 to 75 years	NI	Robotic exoskeleton gait training	Conventional gait training	• There were substantial improvements of timed-up-and-go performance (d=-1.20) and 6MWT (d=0.80) in robotic exoskeleton group. • Exoskeleton training demonstrated substantial improvements in SDMT performance (9.2 points) and thalamocortical resting-state functional connectivity relative to substantial worsening for those who underwent conventional gait training (4.5 points).

Russo M et al. 2018 RCT[46]	45 patients	NI	Robot-assisted gait rehabilitation + virtual reality + traditional rehabilitation	Traditional rehabilitation	• In 6 weeks, the exoskeleton group exhibited substantial improvement (p<0.001) in FIM, TBS and timed-up-and-go. • After 6 weeks, only time-up-to-go was improved (p<0.001). • 1 month after the end of training, a significant worsening in timed-up-and-go was observed in the experimental group (p<0.01).

SR, Systematic review; MA, meta-analysis; RCT, randomised controlled trial; NI, no information; 6MWT, 6-minute walking test; SMD, standardised mean difference; CI, confidence interval; EQ-5D, EuroQol-5D; FAC, Functional Ambulatory Category; ADL, activities of daily living; MAS, Modified Ashworth Scale; FMA, Fugl-Meyer Assessment; K-FES, Korean-modified Falls Efficacy Scale; SD, standard deviation; BBS, Berg Balance Scale; SDMT, Symbol Digit Modalities Test; FIM, Functional Independence Measure; TBS, Tinetti Balance Scale

5.4 Safety

Despite having several reported events such as skin abrasions, oedema[39] and mild bleachable erythema,[44] lower limb exoskeleton was generally safe with no device-related falls or serious adverse events, and well-tolerated by patients during gait therapy.[39,40,41,43,45,46,49,55, level I] This technology was not associated with significant events such as death or hospitalisation.[39]

Numerous data and clinical research supporting this advanced technology have been validated by multiple trials yielding positive outcomes. In addition, the US FDA has authorised medical exoskeletons for walking, gait aid and physical rehabilitation purposes. The FDA classifies medical-powered exoskeletons as Class II devices, code PHL with the exact definition as follows: "A powered exoskeleton is a prescription device composed of an external, powered, motorised orthosis that is placed over a person's paralysed or weakened lower extremity limb(s) for medical purposes."[57] As of March 2023, only two varieties of exoskeletons have been certified for home or personal usage.[58] In addition, the Medical Device Authority Malaysia has recognised three types of lower limb exoskeleton till this date.[59]

5.5 Economic Implication

Two studies reported on cost-effectiveness and one study demonstrated results on budget impact analysis.

Pinto D et al. (2023) conducted a cost-effectiveness analysis to estimate the cost-effectiveness of locomotor training strategies following SCI by injury status (complete versus incomplete) using a practice-based cohort in United States. A prospective, practice-based cohort of four Spinal Cord Injury Model System sites was used to undertake a probabilistic cost-effectiveness analysis. Conventional locomotor training strategies (consisted of treadmill-based with body weight support and overground training) were contrasted with overground robotic locomotor training. The $50,000 USD was a conservative estimate of society's WTP for each extra QALY. Costs were in 2020 United States dollars (USD) and represent the healthcare viewpoint.[47]

Based on the **Table 4**, overground robotic training increased QALY and incurred higher costs for those with complete SCI as compared with incomplete SCI. Besides that, overground robotic training for complete SCI produced the greatest QALY gains albeit had the highest rehabilitation expenses.[47]

Table 4: Diaggregated average costs and effects (standard deviation).[47]

	Conventional training		Overground robotic training	
	Incomplete	Complete	Incomplete	Complete
	N = 57	N = 10	N = 23	N = 9
QALYs	0.045 (0.28)	− 0.044 (0.34)	− 0.032 (0.17)	0.097 (0.20)
Costs	1745 (1741)	2450 (1936)	3867 (4529)	4169) (2276)

QALY, quality-adjusted life year

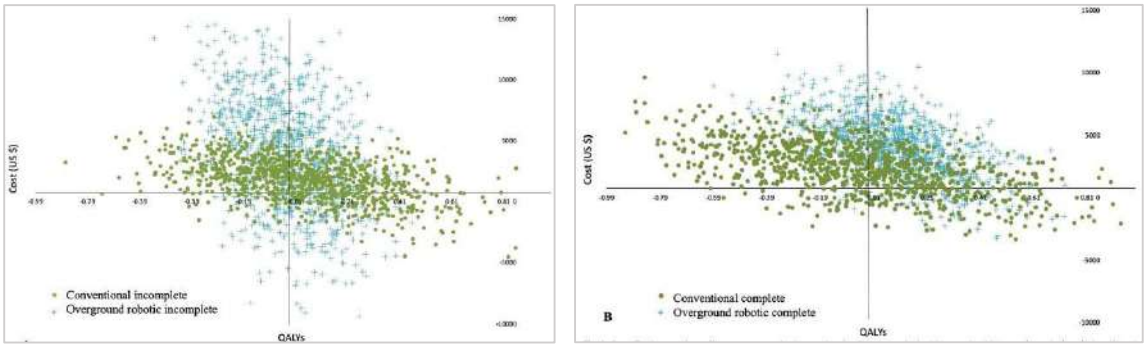
The probabilistic cost-effectiveness analysis generated 1000 simulations to evaluate the uncertainty of cost and effect parameters in the model. Only conventional training for patients with incomplete SCI and overground robotic training for those with complete SCI were found to have a positive net benefit. The cost-effectiveness results are displayed on the cost-effectiveness plane and as acceptability curves in **Figure 15 and 16**.[47]

a) Incomplete SCI

The majority of cost-effectiveness estimates for conventional training for patients with incomplete SCI (43.0%) fell in the right upper quadrant (more effective and more cost), whereas 50.0% of estimates for overground robotic training fell in the left upper quadrant (less effective and more cost) **(Figure 15a)**. Conventional training dominated overground robotic training, indicating it was more effective and less cost on average. Overground robotic training was not the most cost-effective option for an extra QALY at any WTP level **(Figure 16a)**.[47]

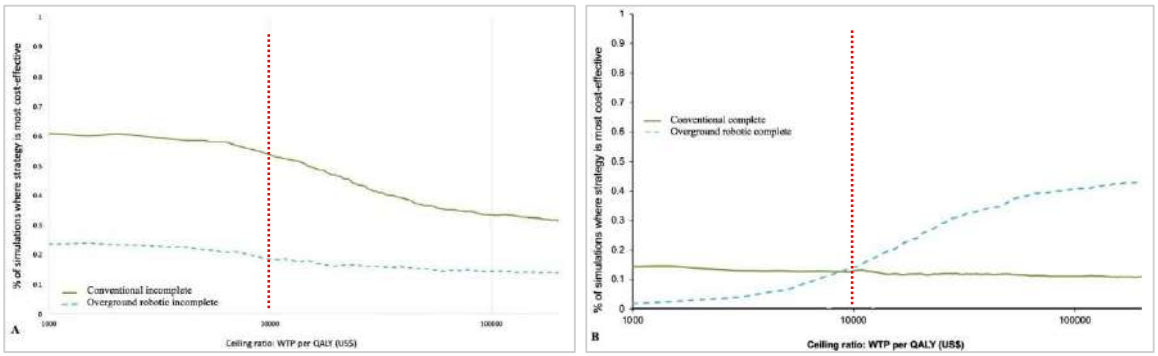
b) Complete SCI

Locomotor strategies for patients with complete injuries follow a pattern in the other direction **(Figure 15b and 16b)**. The majority of cost-effectiveness estimates for conventional training (52.0%) fell in the left upper quadrant (less effective and more cost), whereas 65.0% of estimates for overground robotic training fell in the right upper quadrant (more effective and more cost). Conventional locomotor strategies were most cost-effective when WTP is less than $10,000 USD per QALY. However, when WTP exceeds $10,000 USD per QALY, overground robotic training had the greatest probability of cost-effectiveness. When comparing locomotor strategies in patients with complete SCI, 75.0% of simulations indicated that robotic locomotor training provided the great net benefit.[47]



(a) **(b)**

Figure 15: Cost-effectiveness plane of locomotor strategies (conventional and overground robotic) in people with incomplete spinal cord injury (a) and complete spinal cord injury (b).[47]



(a) **(b)**

Figure 16: Cost-effectiveness acceptability curve of locomotor strategies (conventional and overground robotic) in people with incomplete spinal cord injury (a) and complete spinal cord injury (b).[47]

Menetti S et al. (2020) performed an early cost-effectiveness analysis of a robotic exoskeleton, by modelling its use in both a care home and patients' homes, in addition to United Kingdom (UK)'s standard post-hip fracture care. The population generated in the Markov model was representative of the UK population that sustained a hip fracture between 2003 and 2013. Those studies focused on high-risk subpopulations, such as dementia and cardiovascular disease (CVD; stroke and myocardial infarction). They focused on sex and age-specific risks at ages 65, 75 and 85. The cycle length was one year, with a half-cycle adjustment. Costs (2012/2013 UK pound) and QALYs were discounted at a rate of 3.5% annually. The perspective of the National Health Service in England and personal social services was adopted and the cost-effectiveness threshold was £20,000 per QALY.[48]

In base-case analysis as shown in **Table 5**, the exoskeleton was expected to be cost-effective in CVD patients under the age of 75; ICER on female (£18,753) and male (£19,598). For dementia patients, the exoskeleton was equally cost-effective in avoiding secondary hip fracture, but only in those under the age of 75. The ICER for dementia patients varied between £18,083 (65-year-old female) and £19,900 (75-year-old male).[48]

Table 5: Base-case - Lifetime costs and quality-adjusted life years of cardiovascular disease and dementia hip fractured populations by sex and age.[48]

	Exoskeleton		Usual care		Difference (95% Confidence Interval)		
	Costs	QALYs	Costs	QALYs	Cost	QALYs	ICER
Cardiovascular disease							
Female							
65 years old	£104,735	7.26	£59,588	4.85	£45,147(£41,350 to £49,207)	2.41(1.91 to 2.97)	£18,753
75 years old	£80,067	4.40	£52,210	3.01	£27,857(£26,332 to £29,680)	1.39(1.13 to 1.63)	£20,041
85 years old	£60,162	2.44	£43,972	1.74	£16,190(£15,530 to £16,894)	0.7(0.59 to 0.8)	£23,169
Male							
65 years old	£84,062	5.28	£50,867	3.59	£33,195(£30,346 to £35,895)	1.69(1.32 to 2.09)	£19,598
75 years old	£61,070	2.97	£41,674	2.09	£19,396(£18,188 to £20,534)	0.88(0.69 to 1.04)	£22,122
85 years old	£44,656	1.53	£33,817	1.15	£10,839(£10,332 to £11,355)	0.38(0.32 to 0.44)	£28,467
Dementia							
Female							
65 years old	£105,299	6.14	£60,854	3.68	£44,445(£40,793 to £48,371)	2.46(1.66 to 3.2)	£18,083
75 years old	£80,461	3.74	£53,076	2.29	£27,385(£25,869 to £29,187)	1.44(1.04 to 1.81)	£18,971
85 years old	£60,384	2.10	£44,478	1.34	£15,906(£15,256 to £16,602)	0.75(0.58 to 0.93)	£21,091
Male							
65 years old	£84,393	4.51	£51,668	2.74	£32,725(£29,951 to £35,362)	1.77(1.25 to 2.31)	£18,476
75 years old	£61,303	2.57	£42,208	1.61	£19,094(£17,918 to £20,195)	0.96(0.72 to 1.19)	£19,900
85 years old	£44,801	1.36	£34,134	0.90	£10,667(£10,162 to £11,169)	0.46(0.36 to 0.56)	£23,341

QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio

In terms of leasing, the exoskeleton was not cost-effective until it improved patients' HRQoL by 25.0% and had a hazard ratio of falling of 0.625. However, the lower frequency of second hip fractures did not restrict cost-effectiveness, particularly in less expensive scenarios. The highest hazard ratio of falling that still assured the technologies's cost-effectiveness was 1.125; however, this scenario must be paired with a larger increment in HRQoL (30.0%). In contrast, the prevention of hip fractures had a significant impact in scenarios modelling higher lease fees (e.g. £6,000 annual leasing). These payments could only be justified if the exoskeleton was not inferior to standard treatment and provided a greater average improvement in patients' HRQOL. The proportion of cost-effective scenarios did not change significantly between disease groups, regardless of sex.[48]

Compared to the leasing scenarios, acquiring the device was less likely to be the most cost-effective option. In this regard, HRQoL has a lower effect on the results of the buy scenarios than on the leasing scenarios. In order to be considered cost-effective, the device should improve patients' HRQoL by 48.0% and reduce secondary hip fracture by 50.0%. Similar to the leasing scenarios, the hazard ratio of falling had little influence on the device's cost-effectiveness (i.e. the threshold value was 1.25), but the increment in HRQoL would need to be significantly large, 57.5%. Selling the device was more likely to be a cost-effective choice among patients with dementia, particularly in women under the age of 75.[48]

Meanwhile, a budget impact analysis that was conducted by Pinto D et al. (2020) estimated the budget impact of adding robotic exoskeleton overground training to existing locomotor training strategies in the rehabilitation of people with SCI in the United States. The study was conducted from the perspective of rehabilitation institutions, notably inpatient rehabilitation facilities and long-term care hospitals, which are device purchasers. A retrospective pre-post research design was implemented and the fiscal impact of the exoskeleton was assessed throughout a year. Four SCI Model Systems (Facility A, B, C and D) had committed to participate on this project.[60]

In the base case scenario for all hospital systems, using exoskeleton for locomotor training reduced hospital costs connected with locomotor training delivery. Providing exoskeleton for 10.0% of locomotor training sessions throughout the course of the year reduces yearly locomotor training expenses, ranging from $649 (Facility D) to $4,784 (Facility B); costs were in 2017 USD. The base case scenario was sensitive to a number of characteristics, including the cost of a robotic exoskeleton, the efficiency of robotic exoskeleton use, the training approach used and the lifespan of the exoskeleton device. **Figure 17** depicts a series of one-way sensitivity studies that indicate the range of costs or savings associated with varying parameters across each site. The highest savings were shown in Facility B ($14,704), where the robotic exoskeleton life was prolonged to eight years, while the biggest expense was seen also in Facility B ($52,934), where the adoption rate of robotic exoskeletons was limited to 10.0%. The probabilistic sensitivity analysis took into account the unpredictability of human capital expenses (salary), device cost and locomotor training device replacement.[60]

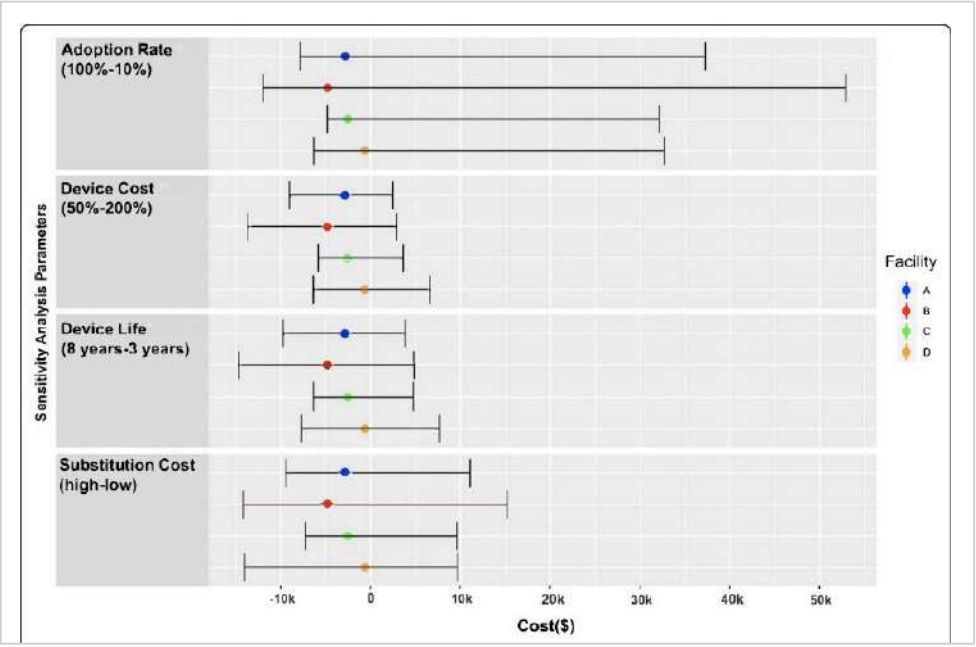


Figure 17: Results from one-way sensitivity analyses. The effect of parameter variation on the base case (depicted as point estimate).[60]

5.6 Partial Economic Evaluation

Method

This partial economic evaluation compares the costs and outcomes of Robot-Assisted Gait Therapy (RAGT) versus conventional therapy for patients requiring rehabilitation for gait therapy. The analysis was performed from the perspective of the healthcare provider, considering all relevant costs associated with both interventions. The cost and effectiveness data were derived from existing studies and expert opinion. The evaluation is based on a treatment cycle of 27 therapy sessions, which is typical for a 9-week therapy cycle (three sessions per week) to make up for one therapeutic unit (1TU). This treatment cycle is also in alignment with a network meta-analysis study that comparing the effectiveness of RAGT with a conventional therapy by Yang FA et al. 2022. In this analysis, conventional therapy refers to standard rehabilitation practices involving manual techniques and non-robotic equipment, such as physical therapist-led exercises and the use of devices like motorised machines, TheraBands and Putty. Both capital costs and recurring costs were considered to calculate the ICER, with effectiveness measured by a SMD.

Key parameters in the analysis included:

i. Session and Duration Assumptions

The evaluation is based on a standardised treatment cycle of 27 therapy sessions, which corresponds to a typical 9-week therapy cycle involving three sessions per week. This treatment cycle is consistent with findings from the Yang FA et al. (2022) study, which compared the effectiveness of RAGT with conventional therapy. Each therapy session for RAGT includes a 30-minute walking session, followed by 15 minutes of adjustment and positioning prior to the session and 15 minutes for removal/ uninstallation after the session, leading to a total duration of approximately one hour per session.

Similarly, conventional therapy, which focuses on improving motor control, sitting, standing stability, gait and ADL, typically takes 30 to 40 minutes per session, with five to 10 minutes required for preparation before and after the session. Both RAGT and conventional therapy are administered two to three times per week, with the maximum number of therapy sessions per week taken into account during the cost calculation.

ii. RAGT and conventional capacities

RAGT: It is assumed that each patient undergoes 720 sessions per year. This is based on three sessions/ day, 5 days/ week, over a 48-week period, allowing for breaks such as holidays or other interruptions. The analysis takes into account practical aspects such as human resource readiness and therapy capacity.

Conventional Therapy: A total of 1200 sessions per year is assumed, based on 5 sessions/day, 5 days/week, over 48 weeks per year. This assumes that the conventional therapy can be more frequently delivered than RAGT, with fewer equipment constraints.

iii. Personnel Requirements

a. RAGT: Each session requires 0.5 personnel per TU. This assumption is based on the idea that the personnel can also operate other advanced rehabilitation technologies concurrently. This aligns with findings by Klobucká (2023), who noted that in reality, during therapy with systems like the Lokomat® in patients with more severe disabilities, a single physical therapist is often responsible for operating other stuffs, effectively reducing the personnel requirement to 0.5 therapists per session. The monthly wage for RAGT personnel is estimated at RM2,580.00, based on the pay scale for *Pegawai Pemulihan Perubatan U41*.

b. Conventional Therapy: Each session requires two personnel per therapeutic unit. The monthly wage for conventional therapy personnel is RM2,400.00, based on the wage for *Jurupulih Perubatan (Fisioterapi) U29* with a *Diploma Lanjutan Rehabilitasi Neuro*.

c. Capital Costs:
Exoskeleton Cost (RAGT): The exoskeleton used for RAGT is assumed to cost RM720,000.00, amortised over a 5-year period. This cost is distributed across the 720 sessions per year, which translates into a per-session cost. The cost of maintenance and training is included within this figure.

Motorised Machine Cost and standing frame (Conventional Therapy): The cost of conventional motorised machines is estimated at RM10,000.00 per year, distributed over the 1,200 sessions per year. The per-session cost for the motorised equipment is calculated based on this annual figure.

d. Consumables:
Consumable Costs (conventional therapy): Consumables such as TheraBands, Putty and other equipment used during therapy sessions are estimated to cost RM1,000.00 per year, distributed over the 1,200 sessions per year. The per-session cost is derived based on the number of sessions conducted annually.

e. Effectiveness Measure:
The effectiveness of RAGT is measured as an improvement in ambulatory function, quantified using the SMD. The effectiveness for RAGT was extracted from a study by Yang FA et al. (2022), where the estimated SMD improvement was 0.3 with a 95%

confidence interval of 0.11 to 0.50. Conventional therapy is considered as the baseline (SMD=0).

Table 5: Baseline Parameters and Assumptions.

Parameter	Value/ Assumption	Details
Total number of RAGT sessions/ year	720 sessions	Three sessions per day, five days per week, 48 weeks per year allowing for breaks such as holidays or other interruptions. Practically in present situation taking into consideration of human resource readiness.
Total number of conventional sessions/ year	1,200 sessions	Five sessions per day, five days per week, 48 weeks per year allowing for breaks such as holidays or other interruptions. Practically in present situation taking into consideration of human resource readiness.
Human resource (RAGT)	0.5 personnel for one TU (in view that the personnel can also operate other advanced rehabilitation technologies at the same time)	Monthly wage = RM2,580.00. *Pegawai Pemulihan Perubatan U41*
Human resource (conventional)	Two personnel for one TU	Monthly wage = RM2,400.00. *Jurupulih Perubatan (Fisioterapi) U29 dengan Diploma Lanjutan Rehabilitasi Neuro*
Exoskeleton cost (RAGT)	RM720,000.00 amortised over five years	Distributed over 720 sessions per year.
Motorised machine cost and standing frame (conventional)	RM10,000.00 per year	Distributed over 1,200 sessions per year.
Consumable cost (conventional)	RM1,000.00 per year	Distributed over 1,200 sessions per year (TheraBands, Putty, etc.).
Effectiveness (SMD, RAGT)	0.3 (95% CI 0.11, 0.5) SMD ambulatory improvement	SMD in ambulatory improvement (Yang FA et al. 2022)

RAGT, Robot-assisted gait therapy; TU, Therapeutic unit; SMD, Standardised mean difference; CI, Confidence interval

f. ICER Calculation:
Incremental cost-effectiveness ratio is calculated by dividing the incremental cost (difference in cost between RAGT and conventional therapy) by the incremental effectiveness (difference in SMD improvement between RAGT and conventional therapy). This provides a measure of the additional cost required to achieve one unit of effectiveness (SMD improvement) using RAGT compared to conventional therapy.

g. Sensitivity Analysis:
To account for uncertainties, a one-way sensitivity analysis was conducted by varying key parameters, such as the number of sessions per year, human resource costs, and effectiveness, within reasonable ranges. The purpose of this analysis was to evaluate the robustness of the ICER and identify the parameters with the greatest impact on cost-effectiveness.

Results

Table 6: Baseline work calculation process and ICER.

Parameter	Value/Calculation	Details
Human resource cost per session (RAGT)	RM1.79	(RM2,580.00 x 0.5) / 720
Human resource cost per session (conventional)	RM4.00	(RM2,400.00 x 2) / 1200
Exoskeleton cost per session (RAGT)	RM200.00	RM720,000.00 amortized over five years, distributed across 720 sessions/year
Motorised machine and standing frame cost per session (conventional)	RM8.33	RM10,000.00 per year, distributed across 1200 sessions per year
Consumable cost per session (conventional)	RM0.83	RM1,000.00 per year, distributed across 1200 sessions per year
Total cost per session (RAGT)	RM201.79	Human resource + exoskeleton cost
Total cost per session (conventional)	RM13.16	Human resource + motorised machine + consumable cost
Total cost for 27 sessions (RAGT)	RM5,449.33	RM201.79 x 27 sessions
Total cost for 27 sessions (conventional)	RM355.32	RM13.16 x 27 sessions
Incremental cost (RAGT vs. conventional)	RM5,094.01	RM5,449.33 to RM355.32
ICER	RM16,980.04 per effectiveness unit (SMD)	Incremental cost / incremental effectiveness = RM5,094.01 / 0.30

RAGT, Robot-assisted gait therapy; SMD, Standardised mean difference

The economic evaluation between RAGT and conventional therapy shows a clear difference in costs when analysed per session. The human resource cost per session for RAGT was calculated at RM1.79, which is derived from a monthly wage of RM2,580.00, with 0.5 personnel required for each session. For conventional therapy, the human resource cost per session is RM4.00, based on a monthly wage of RM2,400.00 and two personnel per session.

The exoskeleton cost per session for RAGT was RM200.00, calculated from a total exoskeleton cost of RM 720,000.00, amortised over five years and distributed across 720 sessions per year. In contrast, the motorised machine and standing frame cost per session for conventional therapy is RM8.33, calculated from an annual cost of RM10,000.00 distributed across 1,200 sessions per year. Additionally, the consumable cost per session for conventional therapy, which includes materials such as TheraBands and putty, is RM0.83 based on an annual cost of RM1,000.00.

When these elements are combined, the total cost per session for RAGT is RM201.79, which consists of human resource and exoskeleton costs. For conventional therapy, the total cost per session is significantly lower at RM13.16, incorporating human resource, motorised machine and consumable costs.

For a standard course of 27 sessions, the total cost for RAGT is RM5,449.33. In contrast, the total cost for 27 sessions of conventional therapy amounts to RM355.32. This results in an incremental cost of RM5,094.01 when comparing RAGT to conventional therapy.

The ICER is calculated by dividing the incremental cost by the incremental effectiveness, which is based on an effectiveness gain of 0.30 SMD for RAGT. The ICER was found to be RM16,980.04 per effectiveness unit (SMD), meaning that for every one-unit improvement in SMD, RAGT incurs an additional cost of RM16,980.00 when compared to conventional therapy.

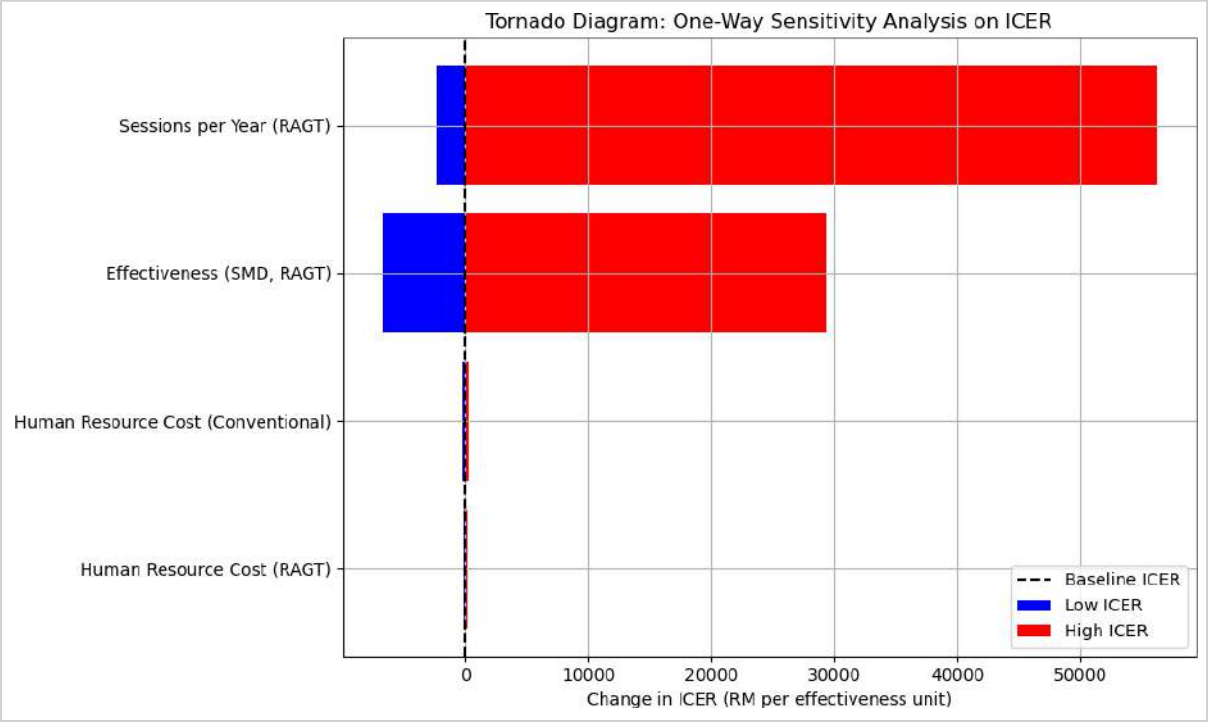


Figure 18: One-way sensitivity analysis

The tornado diagram shows that the number of sessions per year and effectiveness (SMD, RAGT) have the greatest impact on the ICER. For sessions per year, the ICER increases from RM14,660.04 (at 900 sessions per year) to RM73,240.04 (at 600 sessions per year), a change of RM58,580.00, indicating that fewer sessions result in higher costs per effectiveness unit. For effectiveness, the ICER rises from RM10,188.02 (at an SMD of 0.50) to RM46,309.19 (at an SMD of 0.11), a change of RM36,121.17, showing that lower effectiveness significantly decreases cost-effectiveness. These two factors are the most critical in driving ICER variability, while human resource costs have minimal influence.

Scenario Analysis

Scenario	Total Cost (RAGT, 27 sessions)	Total Cost (Conventional, 27 sessions)	Incremental Cost	ICER (RM)
Baseline	RM5,449.33	RM355.32	RM5,094.01	RM16,980.04 per SMD
Scenario 1 (900 sessions/year)	RM4,479.33	RM355.32	RM4,124.01	RM13,746.70 per SMD
Scenario 2 (1 personnel each)	RM5,944.33	RM2,488.83	RM3,455.50	RM11,518.33 per SMD

RAGT, Robot-assisted gait therapy; SMD, Standardised mean difference; ICER, Incremental cost-effectiveness ratio

In Scenario 1, where the number of sessions is increased to 900 sessions per year, the total cost for RAGT drops to RM4,479.33, reducing the incremental cost to RM4,124.01. This results in a lower ICER of RM13,746.70 per SMD, indicating improved cost-effectiveness with a higher number of sessions.

In Scenario 2, where each therapy type uses one personnel instead of the original staffing assumptions, the total cost for RAGT rises to RM5,944.33, while the cost for conventional therapy increases to RM2,488.83. The incremental cost decreases to RM3,455.50, with an ICER of RM11,518.33 per SMD. This scenario shows the best cost-effectiveness, suggesting that staffing adjustments can lead to significant ICER improvements.

5.7 Organisational Issue

Exoskeletons have been utilised and deployed in a variety of sectors as a preventative approach to alleviate workplace musculoskeletal stress. The primary aim of these assistive devices is to deliver mechanical energy to the human body, therefore relieving physical stress on certain body areas. However, there is still dispute about whether employing exoskeletons reduces work-related musculoskeletal problems when workers are handling patients. Exoskeletons must be implemented in the workplace after determining whether they are technically essential and provide a natural solution for the workers, patients and organisations.[61]

While exoskeletons can be useful tools for progress, they should not be used in isolation. Still, it should adhere to the principles and hierarchy of preventive measures, ensuring that their use first and foremost helps to eliminate or control the risk factor identified, and secondly, that their introduction in the workplace does not create new risks for users or third parties, or elicits a rejection response from those who must use them.[62]

Introducing new technology into the workplace necessitates a comprehensive examination of OSH for all parties involved. The Framework Directive (89/391/EEC) requires a design that prioritises human comfort and well-being. The Framework Directive outlines essential duties for organisations and workers. Nonetheless, the workers' responsibilities do not impact the organisation's accountability concept. In this context, the worker shall:[63]

- Make proper use of machinery, apparatus, tools, transportation equipment, other means of production and personal protective equipment.
- Immediately notify the employer of any work scenario that poses a major and urgent hazard, as well as any flaws in the protective procedures.

- Collaborate with the management group in meeting any standards imposed for the protection of health and safety, as well as allowing them to guarantee that the working environment and working conditions are safe and free of hazards.

Due to the diversity in activities done and the association between new technology and musculoskeletal illnesses, ergonomic conditions are not always obvious. It is critical to do an OSH impact study and seek easy solutions to the problem. When all technological options, such as using supplementary lifting equipment or adapting the workspace have been explored, it is vital to address organisational issues, such as reorganising work procedures. Finally, it is possible to consider personal actions to protect workers.[64]

Depending on the specific device, workers must get proper training to utilise exoskeletons successfully and safely. This training may need time and resources. Exoskeletons require constant maintenance to maintain proper operation, which may lead to higher expenses and operational complexity.[64,65] Besides that, user acceptance of the device is essential to its success. The interface between the user and the exoskeleton, as well as the subjective impression of the technology, are critical issues that must be addressed.[66]

5.8 Limitation

The limitations in the review were acknowledged and considered when interpreting the results. The selection of the studies and appraisal was done by one reviewer. The report contains only full-text English papers published in peer-reviewed journals, despite the fact that there was no language constraint throughout the search. This may have resulted in the exclusion of some pertinent articles and further reduced the number of studies.

Additionally, various outcome measures were employed to assess the result of interest in primary research. Several of the selected outcomes overlapped. This terminological difficulty made it impossible to distinguish between outcomes of interest and align specific outcome instruments with specific outcomes. Standardising and adhering to recovery assessment criteria in gait studies may help resolve this issue in the future.

The review's drawback is that only reported statistically significant differences between interventions of interest. A pre-defined minimum clinically significant difference might assist assess the significance of these variations in a clinical setting. Last but not least, using aggregated data in systematic reviews, guidelines or clinical studies with diverse medical devices often results in a loss of detailed qualitative information that could help interpret findings. The information lost includes training intensity, duration and type, as well as its impacts on subpopulations.

However, the evidence synthesis was undertaken in collaboration with clinical experts as part of the guideline working group. Therefore, the results accurately represent the significance of the observed discrepancy.

6.0 CONCLUSION

The comparison between lower limb exoskeletons and conventional rehabilitation highlights both the benefits and challenges associated with each approach. Lower limb exoskeletons can significantly enhance mobility and functional independence, allowing patients to engage in more active rehabilitation with no serious adverse events. They provide consistent support and can facilitate intensive training, which may accelerate recovery for some patients, especially in stroke, SCI and multiple sclerosis patients. However, these devices come with high upfront costs, maintenance expenses and the need for specialised training for both users and clinicians.

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8.0 APPENDICES

8.1 Appendix 1: Literature search strategy

Ovid MEDLINE(R) <2020 to May Week 2 2024>

1	GAIT/	8536
2	gait*.tw.	15371
3	GAIT DISORDERS, NEUROLOGIC/	1423
4	athetotic gait.tw.	0
5	broadened gait.tw.	0
6	charcot* gait*.tw.	0
7	drop foot gait.tw.	2
8	duck gait.tw.	0
9	festinating gait.tw.	5
10	frontal gait.tw.	5
11	hemiplegic gait.tw.	17
12	hysterical gait.tw.	0
13	neurologic ambulation disorder*.tw.	0
14	neurologic gait dysfunction*.tw.	1
15	neurologic locomotion disorder*.tw.	0
16	neurologic gait disorder*.tw.	1
17	rapid fatigue of gait.tw.	0
18	reeling gait.tw.	1
19	rigid gait.tw.	2
20	scissors gait.tw.	0
21	sensorimotor gait disorder*.tw.	0
22	shuffling gait*.tw.	17
23	spastic gait.tw.	52
24	stumbling gait.tw.	2
25	unsteady gait.tw.	117
26	widebased gait.tw.	0
27	ExoMotus M4.tw.	0
28	EXOSKELETON DEVICE/	999
29	exoskeleton device*.tw.	38
30	robotic exoskeleton*.tw.	160
31	ROBOTICS/	8471
32	robotics.tw.	2445
33	soft robotic*.tw.	541
34	telerobotics.tw.	9
35	BIOMECHANICAL PHENOMENA/	19283
36	biomechanic*.tw.	15919
37	biomechanic* phenomena*.tw.	11
38	kinematics.tw.	6079
39	mechanobiological phenomena.tw.	2
40	Lower limb exoskeleton.tw.	95
41	27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39	38697
42	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26	16554
43	41 and 42	4394

OTHER DATABASES

EMBASE Cochrane Library PubMed INAHTA USFDA	Sama MeSH and keywords as per MEDLINE search

8.2 Appendix 2: Hierarchy of evidence for effectiveness/ diagnostic

I	Evidence obtained from at least one properly designed randomised controlled trial.
II-I	Evidence obtained from well-designed controlled trials without randomization.
II-2	Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or research group.
II-3	Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.
III	Opinions or respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees.

SOURCE: US/CANADIAN PREVENTIVE SERVICES TASK FORCE (Harris 2001)

8.3 Appendix 3: Evidence tables

Evidence Table : Effectiveness and safety (Stroke and spinal cord injury) – walking speed, ambulatory, gait distance
Question : What is the effectiveness and safety of lower limb exoskeleton on gait therapy?

Bibliographic citation	Study Type / Methodology	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
1. Nurfarah Aqilah AN, Syaqirah A and Izzuna MMG. ReWalk ReBoot Soft Exoskeleton Device in Stroke Paraplegia Patients. TechBrief Horizon Scanning. Ministry of Health Malaysia: Malaysian Health Technology Assessment Section (MaHTAS); 2022. 13 p. Report No.: 005/2022. Malaysia	**Horizon Scanning** **Objective:** Not mentioned. **Method:** Not mentioned.	I	4 studies 1 systematic review, 1 randomised controlled trial, 1 clinical trial, 1 concept study	Soft exoskeleton (end-effector)	No exoskeleton, no comparator		**Effectiveness** <u>Walking speed</u> • All the exoskeletons were found to be effective in enhancing locomotion, as walking had been possible for people who were unable to walk before. The best result was with the ReWalk which could achieve a speed of 0.51 m/s after 45 training sessions lasting 60 to 120 min. The Indego achieved a speed of up to 0.22 m/s from the first session. The study on Mina did not provide any data on walking speed. Thus, the mobility outcomes reported in the studies showed that exoskeletons was effective for locomotion in a laboratory (all the participants could walk while without the exoskeleton they could not). The ability to perform tasks other than walking and the benefits of wearing the exoskeleton (standing position and exercise) could be enhanced for potential use of lower limb exoskeletons in the community. • Regardless of their reliance on ancillary assistive devices, after only 5 days of walking practice with the device, approximately 61% of study participants increased their exosuit-assisted maximum walking speed by the lower bound of 0.05 m/s, 44% increased by 0.10 m/s, and 22% surpassed the higher bound of 0.16 m/s.22 Study participants also presented with an average 0.07 ± 0.03 m/s ($p = 0.01$) increase in their unassisted maximum walking speed. • The comfortable walking speed was stable at 0.96 m/s prior to training and increased by 0.30 m/s after training. Clinically meaningful increase was seen in maximum walking speed (1: 0.30 m/s) and 6-minute walk test distance (1: 59m). Improvements in paretic peak propulsion (1: 2.80 %BW), propulsive power (1: 0.41 W/kg), and trailing limb angle (1: 6.2 degrees) were observed at comfortable walking speed ($p < 0.05$). Likewise, improvements in paretic peak propulsion (1: 4.63 %BW) and trailing limb angle (1: 4.30 degrees) were observed at maximum walking speed ($p < 0.05$). <u>Ambulatory</u> • Four of seven participants learned to ascend and descend ≥5 stairs with assistance, and these four patients also achieved some outdoor-specific walking skills. Navigating elevators and revolving doors was attempted by four and three participants respectively, and all were successful without assistance. **Safety** • No device-related falls or serious adverse events were reported. • In one trial, it was reported a high incidence of skin issues. Five grade 1 skin aberrations occurred in three participants, and 10 grade 2 aberrations occurred in five participants. All of the skin aberrations resulted in interruptions to the training program, and two participants were forced to withdraw because of recurring skin issues. An additional study participant was required to withdraw	

Evidence Table : Effectiveness and safety (Stroke and spinal cord injury) – walking speed, ambulatory, gait distance
Question : What is the effectiveness and safety of lower limb exoskeleton on gait therapy?

Bibliographic citation	Study Type / Methodology	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
							because of what the authors described as a near serious fracture of a bone in the ankle. • No significant adverse events, such as death or hospitalisation, were reported.	

Evidence Table : Effectiveness and safety (Stroke) – ability to walk, walking speed, gait distance, balance
Question : What is the effectiveness and safety of lower limb exoskeleton on gait therapy?

Bibliographic citation	Study Type / Methodology	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
2. Goetz G, Walter M, Wohlhofner K et al. Robotics and Functional Electrical Stimulation for Stroke Rehabilitation: A Systematic Review of Effectiveness and Safety. AIHTA Project. Report No.: 128. HTA Austria. 2020. Austria	**Systematic Review** **Objective:** To evaluate the potential clinical benefit of robotic assisted rehabilitation with regard to functional outcomes such as ability to walk and activities of daily living. **Method:** The systematic search of the guideline in the database PubMed covered the periods March 2009, November 2013 and July 2017. The overall setting of the guideline takes place in an inpatient, rehabilitative and outpatient care context. Using the Appraisal of Guidelines for Research and Evaluation Instrument (AGREE II) for assessing the methodological quality of the AWMF guideline resulted in the highest possible overall score (7/7). The methodological quality of the included RCTs was assessed by the guideline using a modified version of the PEDro scale being informed by the Oxford Scale. The guideline conducted a qualitative evidence synthesis using the GRADE scheme (Grades of Recommendation, Assessment, Development and Evaluation).	I	17 studies. 1 Cochrane review, 16 primary studies.	Robotic assisted rehabilitation (exoskeletons and end-effectors)	Standard gait rehabilitation		**Effectiveness** a) Stationary exoskeletons Four studies compared robot assisted gait training (RAGT) to conventional physiotherapy or physiotherapy assisted locomotion training. Overall, there is moderate quality evidence that RAGT may not additionally improve ability to walk and balance. Low quality evidence suggests that it may not additionally improve walking speed and gait distance. <u>Ability to walk</u> Ability to walk was reported in three studies (subacute; n=163): none of the studies found a statistically significant difference in ability to walk when comparing RAGT to conventional physiotherapy. <u>Walking speed</u> Walking speed was reported in one study (chronic; n=48): the study did not find a statistically significant difference between rehabilitation with RAGT when compared to physiotherapy assisted locomotion training. <u>Gait distance</u> Gait distance was reported by one study (chronic; n=48): the study did not find a statistically significant difference between rehabilitation with RAGT when compared to physiotherapy assisted locomotion training. <u>Balance</u> Balance was reported by three studies (subacute and chronic; n=174): none of the studies found a statistically significant difference in balance when comparing RAGT to conventional physiotherapy or physiotherapy assisted locomotion training. b) Mobile exoskeletons Two RCTs compared the use of a double-leg exoskeleton and a single-leg exoskeleton. i) Double-leg exoskeleton One study compared a rehabilitation pathway include a HAL robot with weight relief to rehabilitation without HAL. Overall, there is low-quality evidence training with mobile exoskeleton and weight bearing compared to conventional gait training results in no additional improvement in ability to walk, gait distance and balance. <u>Ability to walk</u> Ability to walk was reported by the included study (subacute; n=28): no statistically significant difference was found between groups in FAC or SIS mobility score hereby.	

Evidence Table : Effectiveness and safety (Stroke) – ability to walk, walking speed, gait distance, balance
Question : What is the effectiveness and safety of lower limb exoskeleton on gait therapy?

Bibliographic citation	Study Type / Methodology	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
							Walking speed Walking speed was not reported by the included study. Gait distance Gait distance was reported by the included study (subacute; n=28): no statistically significant difference was found between groups in 2 meters walk test. Balance Balance was reported by the included study (subacute; n=28): no statistically significant difference was found between groups in the berg balance scale. ii) Single-leg exoskeleton For single-leg exoskeleton robots, one study compared gait training with a bionic leg to group training without gait training. Overall, there is low-quality evidence that training with motorized knee single-joint orthosis compared with conventional gait training results in no additional improvement in ability to walk, walking speed, gait distance and balance. Ability to walk Ability to walk was reported by the included study (chronic; n=20): the study did not find a statistically significant difference between rehabilitation with a single-leg exoskeleton and a conventional rehabilitation pathway. Walking speed Walking speed was reported by the included study (chronic; n=20): the study did not find a statistically significant difference between rehabilitation with a single-leg exoskeleton and a conventional rehabilitation pathway. Gait distance Gait distance was reported by the included study (chronic; n=20): the study did not find a statistically significant difference between rehabilitation with a single-leg exoskeleton and a conventional rehabilitation pathway. Balance Balance was reported by the included study (chronic; n=20): the study did not find a statistically significant difference between rehabilitation with a single-leg exoskeleton and a conventional rehabilitation pathway. c) Stationary end-effectors Five studies investigated the use of stationary end-effector gait trainers. Ability to walk Ability to walk was reported in four studies (subacute and chronic; n=331): While two studies [102, 103] found a significant between group difference favouring end-effector based gait training in the subacute stadium, the remaining studies did not find a	

Evidence Table : Effectiveness and safety (Stroke) – ability to walk, walking speed, gait distance, balance
Question : What is the effectiveness and safety of lower limb exoskeleton on gait therapy?

Bibliographic citation	Study Type / Methodology	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
							significant difference between end-effector assisted gait training and conventional gait training. <u>Walking speed</u> Walking speed was reported in five studies (subacute and chronic; n=361): While two studies found a statistically significant between group difference favouring end-effector assisted gait training, the remaining three studies failed to show a statistically significant between group difference. <u>Gait distance</u> Gait distance was reported by four studies (subacute and chronic; n=331): Only one out of these studies found a statistically significant between group difference favouring end-effector based gait training hereby. <u>Balance</u> Balance was reported in two studies (subacute and chronic; n=146): Both studies failed to show a statistically significant between group difference favouring end-effector based gait training. **Safety** Overall, four out of eleven studies reported on safety outcomes with regard to RAR. For stationary exoskeletons, only one out of four includes studies reported on safety outcomes: the RCT reported that no SAEs occurred in 37 patients, of which 20 received RAGT with stationary exoskeletons. No further information were provided with regard to AEs. For mobile exoskeletons, one included RCTs did not report on safety endpoints for double leg exoskeletons. For single-leg exoskeletons, one RCT reported on safety endpoints: no AEs occurred hereby. For stationary end-effectors, two out of five studies reported on safety endpoints: no AEs occurred hereby.	

Evidence Table : Effectiveness (Stroke) – walking test
Question : What is the effectiveness of lower limb exoskeleton on gait therapy?

Bibliographic citation	Study Type / Methodology	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
3. Lo K, Stephenson M and Lockwood C. Effectiveness of Robotic Assisted Rehabilitation for Mobility and Functional Ability in Adult Stroke Patients: A Systematic Review. JBI Database System Rev Implement Rep. 2017: 15(12); 3049-3091. Australia	**Systematic Review and Meta-analysis** **Objective:** To examine the effectiveness of robotic devices in the rehabilitation of stroke patients for upper limb mobility, lower limb mobility, and activities of daily living. The sustainability of treatment effect was also examined. **Method:** The review was limited to randomised and controlled clinical trials. The databases searched included: PubMed, Embase, CINAHL, Cochrane Central Register of Controlled Trials (CENTRAL) and PEDro (Physiotherapy Evidence Database). The rehabilitation program was conducted at hospitals, nursing facilities or across multi-centers and only physical impairments related to upper and lower limbs were considered.	I	Fifty-one studies with 1798 patients. 21 studies evaluated lower limb gait training. Adult stroke patients 18 years and over.	Robotic assisted rehabilitation (exoskeletons and end-effectors)	Conventional training	3 months ≥ x > 3 months	**Effectiveness** Fifteen studies with a total patient population of 701 were analysed. The forest plot showed no significant difference between experimental and control groups. The pooled SMD (random-effects model) was 0.17 (95% CI -0.15 to 0.48, I^2=75%, p=0.31). No evidence for publication bias was found from the funnel plot. Subgroup analysis for acute/ subacute, chronic, severe impairment and moderate/ mile impairment patients • There were no significant differences between experimental and control groups [acute/ sub-acute: SMD 0.24 (95% CI -0.15 to 0.62, p=0.23); chronic: SMD -0.10 (95% CI -0.44 to 0.25, p=0.59); moderate/mild: SMD -0.34 (95% CI -0.97 to 0.29, p=0.29)]. • However, for severe impairment patients, a statistically significant difference favoring the experimental group was found (Figure 12). The pooled SMD (random-effects model) was 0.41 (95% CI 0.19 to 0.63, I^2=28%, p=0.0003). No evidence for publication bias was found from the funnel plot. *Robotic therapy alone versus conventional therapy alone* <u>Walking test</u> • Six studies with a total patient population of 207 were analysed and the result showed no significant difference between experimental and control groups. The pooled SMD (random-effects model) was -0.08, (95% CI -0.74 to 0.58, I^2=80%, p=0.81). The funnel plot showed asymmetry indicative of publication bias. Subgroup analysis for acute/ subacute, chronic, severe impairment and moderate/ mile impairment patients • These showed no significant differences between experimental and control groups [acute/ sub-acute: SMD -0.23 (95% CI -1.43 to 0.96, p=0.70); chronic: SMD 0.03 (95% CI -0.39 to 0.45, p=0.88); severe: SMD 0.40 (95% CI -0.13 to 0.93, p=0.14; moderate/ mild: SMD -0.31 (95% CI -1.13 to 0.51, p=0.46)]. Follow-up (in less than or equal to three months) • Five studies with a total patient population of 259 were analysed. The forest plot showed no significant difference between experimental and control groups. The pooled SMD (random-effects model) was -0.33 (95% CI -1.31 to 0.65, I^2 =92%, p=0.51). A potential for publication bias was found from the funnel plot. Follow up (more than three months) • Six studies with a total patient population of 408 were analysed. The forest plot showed no significant difference between experimental and control groups. The pooled SMD (random-effects model) was 0.30 (95% CI -0.05 to 0.65, I^2=63%, p=0.10). No evidence of publication bias was found from the funnel plot.	

Evidence Table : Effectiveness (Stroke) – ambulation, motor function, balance, walking test, ADL, HRQoL, patient satisfaction
Question : What is the effectiveness of lower limb exoskeleton on gait therapy?

Bibliographic citation	Study Type / Methodology	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
4. Yoo HJ, Bae CR, Jeong H et al. Clinical Efficacy of Overground Powered Exoskeleton for Gait Training in Patients with Subacute Stroke: A Randomised Controlled Trial. Medicine. 2023; 102(4). South Korea	**Randomised Controlled Trial** **Objective:** To investigate the efficacy and usefulness of 12 sessions of overground robot-assisted gait training (RAGT) in subacute stroke patients. **Method:** The study prospectively enrolled patients admitted to the Department of Rehabilitation Medicine of Korea University Anam Hospital between January 2020 and June 2021. All participants underwent conventional daily stroke neurorehabilitation program (90 minutes/day, 5 days/week, for 4 weeks) that included physical and occupational therapy. The conventional program consisted of individualised exercises to improve muscle strength, limb motor function, balance, ability to perform ADL tasks, and gait function. In addition, the patients underwent 12 sessions of gait training (30 minutes/day, 3 days per week, for 4 weeks) according to the group assignment. The intervention group underwent overground RAGT, whereas the control group underwent conventional manual gait training performed by a physiotherapist.	I	17 subacute stroke survivors Intervention (n=9), control (n=8) Age > 18 years	Overground exoskeletal RAGT + conventional training	Conventional training		**Effectiveness** <u>Ability to walk (FAC)</u> • The median value in the analyses of the primary outcome and functional ambulation category (FAC) were relatively higher in the exoskeleton group than in the conventional group; however, the difference was insignificant. <u>Motor function (FMA-LE), Balance (BBS), walking test (10 MWT) and ADL (K-MBI)</u> • In the secondary outcome analyses, the median values of FMA-LE, BBS, 10 MWT, and K-MBI were relatively higher in the exoskeleton group, and TUG was shorter in the exoskeleton group. However, the differences were not statistically significant. <u>HRQoL (EQ-5D)</u> • Only the EQ-5D score was significantly higher in the exoskeleton group after gait training (0.767 in the exoskeleton group, 0.434 in the control group, p=0.028). <u>Ability to walk (FAC) and HRQoL (EQ-5D)</u> • In the between-group analysis, the improvements in the FAC and EQ-5D were statistically higher in the exoskeleton group than in the control group ($p<0.05$). No significant improvement was observed in pulmonary function in either group. <u>Patient satisfaction</u> In particular, the participants were satisfied with the "safety," "comfort," and "effectiveness" domains (median value 4.5, ranging from 3 to 5). On the other hand, some patients reported discomfort in the "weight," "adjustments," and "durability" domains, scoring 2, which indicates that they were not satisfied. None of the participants reported difficulty or discomfort related to the study protocol, nor did any severe adverse events occur during the study period.	

Evidence Table : Effectiveness (Stroke) – gait distance, muscle strength, balance, ADL, muscle spasticity, ambulation + social acceptance
Question : What is the effectiveness of lower limb exoskeleton on gait therapy?

Bibliographic citation	Study Type / Methodology	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
5. Molteni F, Guanziroli E, Goffredo M et al. Gait Recovery with an Overground Powered Exoskeleton: A Randomised Controlled Trial on Subacute Stroke Subjects. Brain Sci. 2021; 11(104). Switzerland	**Randomised Controlled Trial** **Objective:** To investigate the efficacy of o-RAGT in subacute stroke subjects, compared to conventional gait training. **Method:** A total of 120 subacute stroke subjects were recruited from March 2016 to April 2019 in five Italian rehabilitation hospitals. All subjects conducted daily conventional rehabilitation (120 min of rehabilitative intervention six days a week) consisting of physical therapy (e.g., upper limb functional task practice, upper limb muscle strengthening, and exercises for improving balance), speech therapy, and occupational therapy. Moreover, the subjects underwent gait training with a specific protocol, depending on the group assignment: (1) subjects who underwent gait training with the WPE (i.e., the Experimental Group (EG)) and (2) subjects who underwent conventional gait training (i.e., the Control Group (CG)).	I	75 subacute stroke survivors Intervention (n=38); 62.13±8.75 years old, 55% male Control (n=37); 68.24±8.58 years old, 49% male	Wearable powered exoskeleton + conventional training	Conventional training		**Effectiveness** <u>Gait distance</u> The 6MWT increased from 48.60±42.39m(T1) to 139.24±104.7 m (T2) in the EG and from 44.29±59.15 m (T1) to 149.43±130.15 m (T2) in the CG. The study shows the improvement in the 6MWT in both the EG and the CG (p-value < 0.0001). Considering that the 6MWT MCID in subacute stroke subjects is 50.4 m, 55% and 57% of subjects exceeded such values in the EG and the CG, respectively. <u>Muscle strength (MI-AL), balance (TCT), gait distance (10MWT) and ADL (mBI)</u> Similar outcomes were registered for the MI-AL (time effect: p<0.0001; time*grow up effect: p=0.64, TCT (time effect: p<0.0001; time*grow up effect: p=0.28), 10MWT (time effect: p<0.0001; time*group effect: p=0.05), and mBI (time effect: p<0.0001; time*group effect: p=0.66). <u>Muscle spasticity (MAS-AL), ability to walk (FAC and WHS)</u> The MAS-AL did not show any significant intragroup difference, while the FAC and WHS registered a significant number of subjects improving their functional and community ambulation in both groups. These results were confirmed by both the frequentist and Bayesian analyses. **Social acceptance** The subject's usability and acceptance of the WPE were measured with the questionnaire. The results showed that the subjects perceived the robotic treatment positively. Specifically, it was considered comfortable (5.78±1.81), pleasant (5.91±1.50), moderately painful (1.09±2.09), and demanding (2.96±2.10). Moreover, the subjects perceived the WPE as useful (6.22±1.13), they would recommend it (6.35±1.07), and they would like to do further o-RAGT in the near future (5.57±2.23).	

Evidence Table : Effectiveness (Stroke) – clinical measurement, muscle spasticity
Question : What is the effectiveness of lower limb exoskeleton on gait therapy?

Bibliographic citation	Study Type / Methodology	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
6. Park C, Oh-Park M, Bialek A et al. Abnormal Synergistic Gait Mitigation in Acute Stroke Using an Innovation Ankle-knee-hip Interlimb Humanaoid Robot: A Preliminary Randomised Controlled Trial. Scientific Reports. 2021; 11:22823. United States	**Randomised Controlled Trial** **Objective:** To compare the effects of interlimb coordinated humanoid robot (ICT) combined with conventional physical therapy (ICT-C) and conventional physical therapy and gait training (CPT-G) on abnormal spasticity and synergistic gait patterns in acute hemiparesis patients. **Method:** A convenience sample of patients with acute hemiparetic stroke were enrolled as inpatients at the Burke rehabilitation hospital, New York, United states. This module comprises two three-phase direct-current brushless motors, each providing output torque to the hip, knee, and ankle joints. The motors have a drive voltage of 24.0 V, a rated load current of 2.0 A, and a maximum thrust load of 3.8 N. Both groups underwent an additional session of 30 min of therapy daily, 7 days/week, for 2 weeks. The CPT-G group underwent general inpatient treatment, including at least one 60-min session of physical therapy per day. An additional 30-min standard physical therapy session was executed in the pre-ambulatory phase and/or for gait training activities. The ICT-C group underwent general physical therapy, which included at least one 60-min physical therapy session and the additional 30-min ICT session.	I	20 patients with acute hemiparetic stroke (mean age 73.0±12.72 years, 12 women) Age between 18 and 99 years	Hip interlimb coordinated humanoid robot + conventional physical therapy	Conventional physical therapy + gait training		**Effectiveness** <u>Clinical measurements</u> • The paired t-tests showed that the mean post-ICT knee joint angle (M=26.69, SD=1.10) was more increased than the mean pre-ICT knee joint angle (M=22.42, SD=0.61; t(9) =− 14.59; p=0.00) in the ICT-C group, indicating improved knee joint movement after ICT-C in patients with hemiparetic stroke. • The paired t-tests revealed that the mean post-ICT hip active force (M=1.32, SD=0.52; t(9)=−2.56; p=0.03) was significantly greater than the mean pre-ICT hip active force (M=0.59, SD=0.48) in the ICT-C group. The paired t-tests revealed that the mean post-ICT knee active force (M=1.66, SD=1.95; t(9)=−2.47; p=0.04) was significantly greater than the mean pre-ICT knee active force (M=0.05, SD=0.04) in the ICT-C group. The paired t-tests revealed that the mean post-ICT ankle active force (M=1.52, SD=1.06; t(9)=−2.71; p=0.02) was more increased than the mean pre-ICT ankle active force (M=0.46, SD=0.67) in the ICT-C group, indicating an improved hip-knee-ankle joint coordinated force after ICT-C. The standardised effect size index, d, ranged from 0.64 to 0.67, indicating large clinical effects. • The paired t-tests showed that the mean post-ICT hip resistive force (M=2.08, SD=0.11; t(9)=61.61; p=0.00) • was significantly greater than the mean pre-ICT hip resistive force (M=6.18, SD=0.21) in the ICT-C group. The paired t-tests indicated that the mean post-ICT knee resistive force (M=0.12, SD=0.09; t(9)=5.19; p=0.001) was more increased than the mean pre-ICT knee resistive force (M=1.53, SD=0.80) in the ICT-C group. The paired t-tests revealed that the mean post-ICT ankle resistive force (M=−0.07, SD=0.53; t(9)=−4.80; p=0.001) was significantly greater than the mean pre-ICT ankle resistive force (M=−0.84, SD=0.21) in the ICT-C group, indicating an improved hip-knee-ankle joint coordinated force after ICT-C. The standardized effect size index, d, ranged from 0.85 to 1.00, representing large clinical effects. • The paired t-tests showed that the mean post-ICT hip stiffness (M=0.72, SD=0.17; t(9)=1.32; p=0.00) was significantly greater than the mean pre-ICT hip stiffness (M=1.53, SD=0.23) in the ICT-C group. The paired t-tests revealed that the mean post-ICT (M=0.70, SD=0.15; t(9)=7.31; p=0.00) was more increased than the mean pre-ICT knee stiffness (M=1.17, SD=0.11) in the ICT-C group. The paired t-tests revealed that the mean post-ICT ankle stiffness (M=0.40, SD=0.11; t(9)=2.34; p=0.04) was significantly greater than the mean pre-ICT ankle stiffness (M=0.67, SD=0.33) in the ICT-C group, indicating an improved ankle, knee, and hip joint coordinated force after ICT-C. Moreover, the standardised effect size index, d, ranged from 0.68 to 0.95, suggesting large clinical effects. <u>Muscle spasticity (MAS) and Motor Sensor (FMA-LE)</u>	

Evidence Table : Effectiveness (Stroke) – clinical measurement, muscle spasticity
Question : What is the effectiveness of lower limb exoskeleton on gait therapy?

Bibliographic citation	Study Type / Methodology	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
							ANOVA showed significant differences in the hip extensor and ankle dorsiflexor MAS scores between the CPT-G and ICT-C groups (p=0.000; 0.043). The post-hoc analysis confirmed more decreased hip extensor and ankle dorsiflexor spasticity after ICT-C than CPT-G, suggesting that patients with hemiparetic stroke had decreased muscle spasticity after ICT-C but not after CPT-G. ANOVA failed to yield a significant difference in the FMA-LE synergy scale score between CPT-G and ICT-C (p=0.12, 0.17).	

Evidence Table : Effectiveness (Stroke) – locomotor function, motor and balance
Question : What is the effectiveness of lower limb exoskeleton on gait therapy?

Bibliographic citation	Study Type / Methodology	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
7. Lee HJ, Lee SH, Seo K et al. Training for Walking Efficiency with a Wearable Hip-assist Robot in Patients with Stroke: A Randomised Controlled Trial. Stroke. 2019; 3545-3552. South Korea	**Randomised Controlled Trial** **Objective:** To investigate the effects of gait training with a newly developed wearable hip-assist robot on locomotor function and efficiency in patients with chronic stroke. **Method:** The training intervention was conducted for 4 weeks with 3 sessions of training per week. All participants completed a gait training program with a total of 10 sessions comprising 5 treadmill sessions and 5 over-ground gait training sessions with GEMS in the experimental group or without GEMS in the control group.	I	26 patients (stroke with hemiparesis) Age > 20 years old	Hip-assist robot + gait training	Gait training		**Effectiveness** <u>Locomotor function</u> • After completion of 10 training sessions, spatiotemporal gait parameters including gait speed, cadence, and stride length, were significantly improved in both groups. In addition, significant group×time interactions were found for all spatiotemporal gait parameters, and the experimental group demonstrated greater improvement than the control group ($p<0.05$). • Particularly, muscle efforts (% MVC) on the affected side during the gait cycle were significantly improved after gait training for the experimental group, but not in the control group. In addition, positive results were seen in all gait symmetry ratios including temporal step symmetry by 27.88%, spatial step symmetry by 32.97% and a decrease of muscle effort symmetries in RF (45.15%), biceps femoris (48.16%), tibialis anterior (34.20%), and gastrocnemius (34.62%) in the experimental group ($p<0.05$). In contrast, only RF muscle effort symmetry was improved by 27.41% in the control group ($p<0.05$). Significant group×time interactions were observed for all gait symmetry ratios ($p<0.05$). • After 10 intervention sessions the net metabolic energy cost ($mLkg^{-1}\cdot min^{-1}$) was reduced by 14.73% in the experimental group ($p<0.05$) but only by 3.05% in the control group. This demonstrated a significant repeated measures group×time interaction, which meant that training with GEMS was better than without GEMS for improving cardiopulmonary metabolic efficiency after gait training ($p<0.01$). <u>Motor (FMA-LL) and balance (K-FES)</u> After completion of 10 training sessions, experimental group demonstrated greater improvement in Fugl-Meyer Assessment scale-lower limb and K-FES than the control group ($p<0.05$). Significant group×time interactions were also observed for Fugl-Meyer Assessment scale - lower limb and K-FES ($p<0.05$). <u>Relationship between gait symmetry ratio and cardiopulmonary metabolic energy efficiency</u> The reduction in net metabolic energy cost during gait training with GEMS was significantly positively correlated with all gait symmetry ratios ($p<0.01$).	

Evidence Table : Effectiveness (Stroke) – muscle spasticity, step length, balance, patient satisfaction
Question : What is the effectiveness of lower limb exoskeleton on gait therapy?

Bibliographic citation	Study Type / Methodology	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
8. Kang CJ, Chun MH, Lee J et al. Effects of Robot (SUBAR)-assisted Gait Training in Patients with Chronic Stroke: Randomised Controlled Trial. Medicine. 2021; 100(48). South Korea	**Randomised Controlled Trial** **Objective:** to investigate SUBAR-assisted gait training's effects in patients with chronic stroke. **Method:** The study enrolled 30 patients from November 2018 to May 2019 at the Asan Medical Center, a tertiary hospital. This study enrolled patients with FAC 3 or higher for patient safety as a preliminary test of a new ground walking exoskeletal robot. All received 10 treatment sessions for 3 weeks. Each treatment is 30 minutes. A licensed physiotherapist evaluated the parameters before the first treatment and after the final treatment. The conventional physiotherapy was based on traditional neurodevelopmental treatment techniques. Patients practiced passive and active range of motion exercises, strengthening exercises, sitting and standing balance, sit-to-stand movement, and functional gait training. SUBAR differs from the well-known exoskeleton-type robot Lokomat. SUBAR has a length, width, and height of about 140cm, 140cm, and 130cm, respectively. It does not need to be fixed, nor does it require a large space for installation, so it is applicable in hospital corridors.	I	Age ≥ 18years old 30 patients Intervention (n=15), control (n=15)	Walking exoskeletal robot	Conventional physiotherapy		**Effectiveness** <u>Muscle spasticity (MAS), step length, balance (BBS)</u> In the SUBAR group, MAS and step length were significantly improved after treatments. The SUBAR group also showed greater improvement in stride length, but not significantly. In the control group, there were significant improvements after treatments in the BBS, the MAS, and stride length. For step length of the affected limb, the SUBAR group showed greater improvement than the control group, but these results did not differ significantly. The BBS improved more in the control group than in the SUBAR group. There were no differences in other measurements between the 2 groups. <u>Patient satisfaction</u> Treatment satisfaction in the SUBAR group, as indicated by the self-questionnaire, was 3.6 out of 4 points. Scores for the training time and number of sessions were 3.20 and 3.00, respectively. Some patients gave 2 points because of the short time and number of sessions.	

Evidence Table : Effectiveness and safety (Stroke) – gait assessment, balance, QoL, gait distance, steps number
Question : What is the effectiveness and safety of lower limb exoskeleton on gait therapy?

Bibliographic citation	Study Type / Methodology	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
9. Jayaraman A, O'Brien MK, Madhavan S et al. Stride Management Assist Exoskeleton vs Functional Gait Training in Stroke. Neurology. 2019; 92(3). United States	**Randomised Controlled Trial** **Objective:** To test the hypothesis that gait training with a hip-assistive robotic exoskeleton improves clinical outcomes and strengthens the descending corticospinal drive to the lower limb muscles in persons with chronic stroke. **Method:** Trial participants were recruited between November 2013 and November 2014 from the Shirley Ryan AbilityLab (Chicago) and 2 satellite clinics: Willowbrook Outpatient and DayRehab Center (Willowbrook, Illinois) and Northbrook Outpatient Center (Northbrook, Illinois). Some were recruited following outpatient care and others from the community, with varied times since stroke. Intervention consisted of therapist-guided gait training at 45 minutes per session, ;3 times per week for 6-8 weeks (18 sessions total). This amount was chosen per Medicare reimbursement guidelines for standard outpatient stroke rehabilitation. All sessions were administered by a licensed physical therapist.	I	50 patients Intervention (n=25), control (n=25) Age 18 to 85 years old	Overground gait training with exoskeleton	Intensity-matched functional gait training	3 months	**Effectiveness** <u>Gait assessment (Functional gait assessment), balance (balance confidence and falls), QoL</u> The SMA group demonstrated improvement from pre in functional gait, balance confidence, and falls efficacy at Mid, which were not seen for FTST. The FTST group demonstrated improvement from pre in quality of life at Mid and Fol, which were not seen for SMA. <u>Gait distance (6MWT), balance (BBS)</u> There were main effects of intervention on percentage change of walking endurance in the 6MWT (p=0.030) and balance in the BBS (p=0.036), wherein the SMA group demonstrated greater improvements than the FTST group. At Post, distance covered in the 6MWT improved on average (SD) by 46.0% (27.4) for SMA, compared with 35.7% (20.8) in FTST. Balance improved most for participants with hemorrhagic stroke in the SMA group, and this was significantly greater than that of the same subtype in FTST (p=0.029). At Post, BBS scores improved by 24.7% (20.1) and 6.1% (4.0) in the SMA for hemorrhagic and ischemic subtypes, respectively, compared with 6.8% (6.7) and 7.7% (7.3) in FTST. There was no effect of intervention on percentage change for any other outcomes, including the primary outcome of self-selected walking speed. <u>Steps number</u> On therapy days, participants training with the SMA device took more steps and worked at a higher activity level than FTST participants. Average (SD) daily step count on therapy days was 3,028 (1,510) steps for the FTST group and 4,366 (2,426) steps for the SMA group, with a main effect of intervention (p=0.013). This corresponds to an average (SD) step increase of 23% (67) for the FTST group and 46% (88) for the SMA group relative to the first day of therapy, with a main effect of intervention (p=0.044). Relative to their average step count on non-therapy days, participants increased their step count on therapy days by 61.4% (43.5) in FTST and 88.0% (82.4) in SMA. **Safety** No adverse events in either intervention group.	

Evidence Table : Effectiveness and safety (Stroke) – gait quality, step cadence, gait cycle duration, stance/ swing ratio, muscle activation, motor pathways, motor skills
Question : What is the effectiveness and safety of lower limb exoskeleton on gait therapy?

Bibliographic citation	Study Type / Methodology	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
10. Calabro RS, Naro A, Russo M et al. Shaping Neuroplasticity by Using Powered Exoskeletons in Patients with Stroke: A Randomised Clinical Trial. Journal of NeuroEngineering and Rehabilitation. 2018; 15(35). Italy	**Randomised Controlled Trial** **Objective:** To assess whether Ekso™ is useful in improving functional ambulation capacity and gait performance in chronic post-stroke patients compared to conventional OGT. **Method:** Eligible patients were selected among those who attended the Neurorobotic Rehabilitation Unit between May and August 2017. Both the groups were provided with conventional physiotherapy training (including a 15-min warm-up and cool-down period), scheduled in five sessions per week for eight consecutive weeks, 60 min for each session. In addition to conventional physiotherapy training, EGT patients practiced 45-min session of Ekso™ training, while OGT patients underwent 45-min of conventional gait training, for all 8 weeks.	I	Age ≥ 55 years old (to avoid cases of young stroke) 40 patients Intervention (n=20), control (n=20)	Exoskeleton gait training + overground gait training	Overground gait training		**Effectiveness** <u>Gait quality, step cadence, gait cycle duration, stance/ swing ratio</u> Specifically, the gait quality index (time×group $F_{(1,38)}$=43, p<0.001, d=0.9) and the step cadence (time×group $F_{(1,38)}$=17, p<0.001, d=0.9) improved more in the EGT than OGT. Also, it was observed more evident reduction of the gait cycle duration (time×group $F_{(1,38)}$=17, p<0.001, d=0.9) and more evident increase in stance/swing ratio (time×group $F_{(1,38)}$=8.6, p=0.008, d=0.8) in the affected limb in EGT than OGT. In parallel, we found a more evident shortening of gait cycle duration (time×group $F_{(1,38)}$=12, p<0.001, d=0.9) and a decrease of stance/swing ratio in the unaffected limb (time×group $F_{(1,38)}$=14, p<0.001, d=0.9) in EGT than OGT. <u>Muscle activation</u> In particular, the EMG amplitude of paretic muscles over the entire gait cycle at TPOST were affected more in EGT (time×muscle $F_{(3,57)}$=4.3, p=0.007, d 0.8) than OGT group (time×muscle $F_{(3,57)}$=2.8, p=0.04, d=0.6), as compared to the non-paretic ones. Specifically, we found a significant RMS decrease in the affected and unaffected RF and the unaffected BF, and a magnitude increase in the affected BF and the affected and unaffected S (post-hoc p-values significant when p<0.008). Both TA muscles showed non-significant changes, except a trend to an increased activation in the paretic TA muscle in the EGT group (p = 0.01). <u>Motor pathways</u> Following rTMS, MEP amplitude in the affected hemisphere increased more in EGT than OGT (time×group $F_{(3,114)}$=5.7, p=0.001; d=0.8), whilst SMI strength equally decreased (i.e., conditioned MEP amplitude increased) in both groups (time×group p=0.4), given that SMI strength was different between the groups already at the TPOST baseline. MEP amplitude in the unaffected hemisphere slightly decreased only in the EGT group (time×group $F_{(3,114)}$ =4, p=0.01, d=0.6), whilst SMI strength increased more (i.e., conditioned MEP amplitude decreased) in EGT than OGT (time×group $F_{(3,114)}$=5.8, p=0.001, d=0.8), despite SMI strength being different between the groups already at the TPOST baseline. <u>Motor skills</u> • Altogether, EGT induced a rebalance of the SMI of the affected and unaffected hemispheres, in parallel to CSE interhemispheric remodulation, whereas OGT acted more on the affected than unaffected hemisphere. • In detail, only EGT increased PF-SMA connectivity in the unaffected hemisphere (time×group $F_{(1,38)}$=4.6, p=0.03, d=0.7), the ipsilateral (time×group $F_{(1,38)}$=18, p<0.001, d=0.9) and contralateral PF-P (time×group $F_{(1,38)}$=8.5, p=0.006, d=0.8) and the contralateral PF-O connectivity within the unaffected hemisphere (time×group $F_{(1,38)}$=7.8, p=0.008, d=0.9). EGT induced a more evident improvement in ipsilateral and contralateral PF-CP (time×group $F_{(1,38)}$=13, p=0.001, d=0.9) and PF-SMA in the affected hemisphere (time×group $F_{(1,38)}$=26, p<0.001, d=0.9) as compared to OGT.	

Evidence Table : Effectiveness and safety (Stroke) – gait quality, step cadence, gait cycle duration, stance/ swing ratio, muscle activation, motor pathways, motor skills
Question : What is the effectiveness and safety of lower limb exoskeleton on gait therapy?

Bibliographic citation	Study Type / Methodology	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
							Safety All participants completed the training without any significant adverse events, except a mild skin bleachable erythema at the thigh and shank strap locations in seven patients of the EGT.	

Evidence Table : Effectiveness and safety (Stroke) – ability to walk, walking speed, limb/ muscle strength, balance, ADL
Question : What is the effectiveness and safety of lower limb exoskeleton on gait therapy?

Bibliographic citation	Study Type / Methodology	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
11. Nam YG, Lee JW, Park JW et al. Effects of Electromechanical Exoskeleton-assisted Gait Training on Walking Ability of Stroke Patients: A Randomised Controlled Trial. Archives of Physical Medicine and Rehabilitation. 2018. Republic of Korea	**Randomised Controlled Trial** **Objective:** To assess the efficacy of electromechanical exoskeleton-assisted gait training on walking ability of stroke patients based on ambulatory function, muscle strength, balance, gait speed, and capacity. **Method:** From October 4 2016, to December 31 2016, 40 individuals with stroke were contacted and invited to join the study. The experimental group performed electromechanical-assisted gait training for 30 minutes by Exowalk. The control group performed physical therapist-assisted gait training for 30 minutes by conventional method. Both groups continued to follow similar traditional physical therapy except gait training. Traditional physical therapy consisted of joint range-of-motion exercise, muscle strengthening exercise, sit-to-stand and stand-to-sit, balance exercise, and any other exercise except gait training. Gait training was performed by therapeutic intervention for 5 days a week for a period of 4 weeks.	I	Age > 19 years old N=36 Intervention: 18 Control: 16	Electromechanical exoskeleton-assisted gait training + traditional physical therapy	Traditional physical therapy		**Effectiveness** <u>Ability to walk (FAC and RMI), walking speed (10MWT), limb/ muscle strength (MI), balance (BBS), ADL (MBI)</u> • FAC in the control group was 2.44±1.55 in the pretraining and 2.75±1.53 in the post-training. FAC in the experimental group was 3.22±1.31 in the pretraining and 3.78±1.44 in the post-training. • Although FAC improved after gait training in both groups, the change in FAC between pre- and post-training was statistically significant in the experimental group alone. Most secondary outcome measures showed improvement after gait training. Between pretraining and post-training, the changes in outcome measures such as RMI, 10MWT, MI, BBS, and MBI in the control group, and FAC, RMI, 6MWT, MI, and BBS in the experimental group were statistically significant. • The difference in FAC change between pretraining and posttraining was 0.20±0.17 in the control group and 0.64±0.16 in the experimental group. The difference in FAC change between 2 groups was not statistically significant, although the altered FAC in the experimental group was statistically significant unlike the control group. The differences in outcomes between 2 groups were not significant after adjusting the data by age and duration. • FAC was negatively correlated with the duration after stroke in experimental groups (FAC, r=-0.507; p<0.05). **Safety** No adverse events were noticed during gait training in either group.	

Evidence Table : Effectiveness and safety (Stroke) – walking speed, walking time, cadence, stance time, swing time, step length, stride length, temporal asymmetry
Question : What is the effectiveness and safety of lower limb exoskeleton on gait therapy?

Bibliographic citation	Study Type / Methodology	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
12. 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. Journal of NeuroEngineering and Rehabilitaion. 2015; 12(69). United States	**Randomised Controlled Trial** **Objective:** To compare the effects of the Stride Management Assist (SMA®) System, a new wearable robotic device developed by Honda R&D Corporation, Japan, with functional task specific training (FTST) on spatiotemporal gait parameters in stroke survivors. **Method:** Subjects were recruited from the Chicago area. Based on their convenience and ability to commute, subjects were referred to one of the Rehabilitation Institute of Chicago (RIC) outpatient stroke rehabilitation clinics, either in downtown Chicago, or in the suburbs of Northbrook, IL, or Willowbrook, IL. Training sessions were completed by licensed RIC clinical physical therapists. Subjects in both groups received training 3 times per week for 6-8 weeks, for a maximum of 18 training sessions. Each session was directed by a licensed physical therapist and lasted 45 min. Gait assessments were performed at visits 0 (baseline), 10 (mid-test) 18 (posttest), and at 3 months (follow-up) after training. Participants did not receive any other therapy sessions during the 3-month follow-up period.	I	50 patients (33 males, 17 females) with chronic stroke Intervention (n=25; 17 males, 8 females) Control (n=25; 16 males, 9 females) Age 18 to 85 years old	Wearable exoskeleton	Standard physical therapy (all patients chose improvement in gait function as functional goal)	3 months	**Effectiveness** In the SMA group, step length values on the impaired side during the self-selected walking speed trials were significantly longer, and spatial asymmetry during fast-walking speed trials was significantly lower than in the FTST group. No other significant differences between groups were observed during either self-selected velocity or fast-velocity trials. Both the SMA and FTST training groups showed significant within-group improvements in numerous gait parameters. However, within the SMA group, significant improvements in additional spatiotemporal variables were observed compared to the FTST group: <u>Walking speed</u> In self-selected walking velocity trials, significantly improved gait speeds were achieved in both groups. Both groups had statistically significant increases in walking speed at mid-, post- and follow-up testing compared to baseline values. However, in addition, in the SMA group, significant improvements were also observed between mid- and post-test walking speed velocity ($p<0.008$). In fast-velocity walking trials, both groups showed significant increases in gait velocity at mid-, post-, and follow-up testing compared to baseline and between the mid- and post-testing time points ($p<0.008$). <u>Walking time</u> • In self-selected walking velocity trials, step times were significantly lower at post-test compared to baseline on the impaired side in both the training groups ($p< 0.008$). • On the non-impaired side, for the FTST group, step times were significantly lower at the post-test when compared to baseline ($p<0.008$). However, non-impaired step times were significantly lower at both mid- and post-tests compared to baseline only in the SMA group ($p<0.008$). • In fast-velocity walking trials, the FTST group showed significantly lower step times at post-test compared to baseline and mid-test for the impaired side ($p<0.008$), and on the non-impaired side, post-test values were lower than baseline ($p< 0.008$). However, the SMA group had significantly lower step times at mid-, post-, and follow-up testing compared to baseline in both impaired and non-impaired sides ($p<0.008$). <u>Cadence</u> During self-selected walking speed trials, a significant increase in cadence was observed only at post-test compared to baseline ($p< 0.008$) in the FTST group. However, in the SMA group, significant changes were also seen at mid- and post-test compared to baseline ($p<0.008$). For fast-walking trials, the FTST group had a significant increase in cadence at post-test compared to baseline ($p< 0.008$) and between post- and mid-test ($p<0.008$). In the SMA group, cadence at mid-, post- and follow-up testing was also significantly increased over baseline ($p <0.008$).	

Evidence Table : Effectiveness and safety (Stroke) – walking speed, walking time, cadence, stance time, swing time, step length, stride length, temporal asymmetry
Question : What is the effectiveness and safety of lower limb exoskeleton on gait therapy?

Bibliographic citation	Study Type / Methodology	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
							Stance time • In self-selected walking speed trials, the FTST group showed significant reduction in stance time on both the impaired and non-impaired sides at post-test compared to baseline (p<0.008). However, for the SMA group, a decreased stance time was observed at mid-, post- and follow-up testing on both the impaired and non-impaired sides (p<0.008). Furthermore, a significant decrease was identified between mid- and post-test stance times on the non-impaired side (p <0.008). • During fast-velocity walking trials, the FTST group had significantly shorter stance times at post- and follow-up testing compared to baseline on both the impaired and non-impaired side. In addition, the non-impaired side also had a significant decrease at post- compared to mid-test values (p<0.008). However, in the SMA group, stance time decreased significantly at mid-, post- and follow-up testing compared to baseline on both the impaired and non-impaired sides (p<0.008). Swing time In self-selected walking speed trials, swing time decreased significantly on the impaired side at post-test compared to baseline value in the SMA group (p<0.008), while no significant changes were observed in the FTST group. In fast-velocity walking trials, swing time was significantly decreased at follow-up compared to baseline on the impaired side in the FTST groups (p<0.008). In contrast, in the SMA group, significant decreases were observed at mid-, post- and follow-up tests on the impaired side (p<0.008). Swing times at follow-up on the impaired side were significantly lower compared to mid- and post-test values in both groups (p<0.008). No changes were observed on non-impaired sides in either group. Step length • During self-selected walking speed trials, subjects showed a significant increase in step length at mid- and post-tests compared to baseline on the impaired side and non-impaired sides in both training groups (p<0.008). Additionally, in the SMA group, a significant increase in step length was also found at follow up vs. baseline and post vs. mid time points on the impaired side. The non-impaired side had significant increases at follow-up when compared to both pre- and mid- values in the FTST group, (p<0.008). • In fast-pace walking trials, the impaired side in both groups showed an increase in step length at mid-, post, and follow-up tests from baseline level (p<0.008). In addition, in the SMA group, impaired-side step length increased significantly from mid- to post-test (p<0.008). • On the non-impaired side, an increase in step length was observed at mid-and post-tests compared to baseline in both training groups. Additionally, the FTST group showed significant increases in step length between baseline and follow-up, and mid-time points vs. post and follow-up.	

Evidence Table : Effectiveness and safety (Stroke) – walking speed, walking time, cadence, stance time, swing time, step length, stride length, temporal asymmetry
Question : What is the effectiveness and safety of lower limb exoskeleton on gait therapy?

Bibliographic citation	Study Type / Methodology	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
							Stride length • During the self-selected walking speed trials, impaired and non-impaired sides showed a significant increase in stride length at mid-, post- and follow-up testing points compared to baseline in both the FTST and SMA groups ($p<0.008$). In addition, in the SMA group, the increase between mid- to post- was also significant on both sides ($p<0.008$). • Similar results were observed in fast-pace walking trials, where both impaired and non-impaired sides showed a significant increase in stride length at mid-, post- and follow-up compared to baseline. Stride-length in the FTST group also increased significantly from mid- to follow-up values for both the impaired and non-impaired sides. In the SMA group the increase observed from mid- to post- was significant on both sides ($p<0.008$). Temporal asymmetry Within the SMA group, a significant decrease in temporal asymmetry was observed at post-testing compared to baseline, for both self-selected and fast walking velocity trials ($p<0.008$). No significant decrease in temporal asymmetry was observed within the FTST group. **Safety** No adverse events were reported during the entire duration of the study.	

Evidence Table : Effectiveness and safety (Spinal cord injury)
Question : What is the effectiveness and safety of lower limb exoskeleton on gait therapy?

Bibliographic citation	Study Type / Methodology	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
13. Yang FA, Chen SC, Chiu JF et al. Body Weight-supported Gait Training for Patients with Spinal Cord Injury: A Network Meta-analysis of Randomised Controlled Trials. Scientific Reports. 2022; 12: 19262.	**Systematic Review and Network Meta-analysis** **Objective:** To assess the effect and priority of each training protocol related to body weight-supported overground training (BWSOGT), body weight-supported treadmill training (BWSTT), and robot-assisted gait training (RAGT). **Method:** The researchers searched the PubMed, Cochrane Library, Scopus, and Embase databases for relevant articles from inception to 6 August 2022. The following data were obtained from each RCT: RCT type, American Spinal Injury Association Impairment Scale (AIS) grade, number and mean age of participants, protocol used in different groups, treatment duration, and outcome measurements. Network plots contain nodes, which represent the interventions in the network, and lines, which highlight the available direct comparisons between pairs of interventions. The size of nodes and the width of lines both represent the number of studies. Our network plot depicts two triangle loops (RAGT-BWSTT-control intervention and BWSTT-BWSOGT-control intervention), and the loop-specific heterogeneity revealed no significant inconsistency between the results of direct and indirect comparisons.	I	15 studies 497 patients	Robot-assisted gait training Weight-supported overground Weight-supported treadmill training	Conventional gait training; sit to stand, static and dynamic standing balance, weight shifting, walking, turning, and stand to sit		**Effectiveness** • Figure 3 presents a network diagram of the included body weight-supported gait training therapies. At least one placebo-controlled trial was included for each therapy. The pooled SMDs of functional scores in the network meta-analysis revealed that RAGT was significantly more favourable than the control intervention, whereas BWSTT and BWSOGT did not result in significant differences compared with the control intervention. The SMDs and 95% CIs from comparisons between the control intervention and other body weight-supported gait training therapies were as follows: RAGT = 0.30 (0.11 to 0.50), BWSTT = 0.09 (− 0.40 to 0.58), and BWSOGT = 0.09 (− 0.55 to 0.73; Fig. 4). • Moreover, we synthesised head-to-head studies separately to assess differences among body weight-supported gait training strategies. Table 2 presents the results of the pairwise meta-analysis and network meta-analysis of walking ability with overall training. • Furthermore, the distribution of probabilities in the ranking of each training strategy was analysed. The ranking probabilities indicated that RAGT was the most effective, followed by BWSOGT, BWSTT, and the control intervention (Fig. 5). **Safety** Of the 15 selected RCTs, six reported on adverse events. No adverse events were observed in four studies and two reported that some participants had experienced pain. The investigated interventions were relatively safe and well tolerated by participants.	

Evidence Table : Effectiveness and safety (Spinal cord injury) – walking speed, gait distance, balance
Question : What is the effectiveness and safety of lower limb exoskeleton on gait therapy?

Bibliographic citation	Study Type / Methodology	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
14. Edwards DJ, Forrest G, Cortes M et al. Walking Improvement in Chronic Incomplete Spinal Cord Injury with Exoskeleton Robotic Training (WISE): A Randomised Controlled Trial. Spinal Cord. 2022; 60: 522-532. United States	**Randomised Controlled Trial** **Objective:** To demonstrate that a 12-week exoskeleton-based robotic gait training regimen can lead to a clinically meaningful improvement in independent gait speed, in community-dwelling participants with chronic incomplete spinal cord injury (iSCI). **Method:** Between September 26 2016 and September 3 2019, across seven US sites (6 main study, 1 run-in), 45 participants were enrolled, of which 33 were randomized to the main study and 12 enrolled as run-in participants. Participants could volunteer for the study if they had motor incomplete upper motor neuron paraplegia or tetraplegia, from traumatic or non-traumatic injury at least one year prior, and self-selected gait speed of <0.44 meters/second (m/s) with the ability to take at least one step. One to three participants per site were required to complete the Ekso intervention protocol as run-in participants, to ensure that assessment and training procedures were practiced and followed as required in the clinical trial protocol.	I	33 patients Intervention (Ekso group) (n=14), Control A (active control) (n=10), Control B (passive control) (n=6)	Exoskeleton gait training	Standard gait training No gait training		**Effectiveness** <u>Walking speed</u> • Self-selected gait speed following the 12-week intervention increased in the Ekso group by 51% (mean, SD; 0.18±0.23 m/s) Active Control by 32% (0.07±0.11 m/s) and Passive Control 14% (0.03±0.03 m/s), within group and between group comparisons p>0.05. Maximal gait speed following the 12-week intervention increased in the Ekso group by 44% (0.20±0.24 m/s) Active Control 50% (0.14±0.18 m/s) and Passive Control 14% (0.03±0.13 m/s) within group and between group comparisons p>0.05. The highest individual absolute speed improvement at both self-selected and fast speeds was seen in the Ekso group. There was a marginal effect of improving by repeated testing as seen in the Passive Control group. Mean improvement in walking speed for both intervention groups at the follow-up visit were not statistically significant (p>0.05). Improvement above the MCID (0.15m/s) during the self-selected speed test was examined between groups, with the highest responder proportion in the Ekso group at 3 of 9 or 1/3 of participants, 2 of 10 or 1/5 in the Active Control, and 0 in the Passive Control group (between-group difference in proportions p> 0.05). <u>Gait distance (6MWT) and balance (TUG)</u> • The median distance covered in the 6MWT following the 12-week intervention was 538.0 feet (Quartile 268.0 to 687.3) for the Ekso Group, 346.6 feet (Quartile 219.5 to 711.5) for the Active Control, and 320.0 feet (Quartile 148.8 to 466.6) for the Passive Control representing improvements of 34%, 28%, and 18%, respectively. • The median time for TUG following intervention was 26.4 s (Quartile 17.3 to 53.0), for the Ekso group, 30.0 s (Quartile 26.0 to 70.7) Active Control, and 46.0 s (Quartile 29.0 to 64.9) for the Passive Control, representing improvements of 18.7%, 19.9%, and 12.7% respectively. • Within-group and between-group differences were not significant (p>0.05) for both the 6MWT and TUG measures. **Safety** • Three SAEs occurred during the trial: two were urinary tract infections (UTI) unrelated to the device, and one participant in the active group was admitted to a hospital with lower extremity numbness and a UTI. The numbness was deemed by the DSMB to be "possibly related" to the Active BWSTT group. No falls occurred during training or evaluation sessions in any group. • From the total sample of 45 participants (run-in plus main study participants), adverse events that were deemed "possibly" or "probably" related to the device or training include the following: 12 (8 Ekso, 4 Active) upper and lower extremity musculoskeletal issues, including orthopedic pain; 4 (3 Ekso, 1 Active) neurological issues, including increased spasticity; 6 (5 Ekso, 1 Active) skin issues; and 1 (Ekso) visceral issue. Three of these were considered severe: 2	

Evidence Table : Effectiveness and safety (Spinal cord injury) – walking speed, gait distance, balance
Question : What is the effectiveness and safety of lower limb exoskeleton on gait therapy?

Bibliographic citation	Study Type / Methodology	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
							musculoskeletal (1 Ekso, 1 Active) and 1 neurological (Ekso). Ten of these AEs were deemed "unanticipated" possibly related to Ekso training (8) or BWSTT (2). In summary, active training was generally well tolerated, with several mixed AE reported in both groups.	

Evidence Table : Budget impact analysis (Spinal cord injury)
Question : What is the budget impact of lower limb exoskeleton on gait therapy?

Bibliographic citation	Study Type / Methodology	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
15. Pinto D, Garnier M, Barbas J et al. Budget Impact Analysis of Robotic Exoskeleton Use for Locomotor Training Following Spinal Cord Injury in Four SCI Model Systems. Journal of NueuroEngineering and Rehabilitation. 2020; 17(4). United States	**Budget Impact Analysis** **Objective:** To estimate the budget impact of adding robotic exoskeleton over-ground training to existing locomotor training strategies in the rehabilitation of people with spinal cord injury. **Method:** A Budget Impact Analysis (BIA) was conducted using data provided by four Spinal Cord Injury (SCI) Model Systems rehabilitation hospitals. Hospitals provided estimates of therapy utilization and costs about people with spinal cord injury who participated in locomotor training in the calendar year 2017. For the purpose of this study, we evaluate a model that reflects the introduction or expansion of RTexo on the total health system budget at four model health systems with different case mixes. Interventions were standard of care walking training including body-weight supported treadmill training, overground training, stationary robotic systems (i.e., treadmill-based robotic gait orthoses), and overground robotic exoskeleton training. The main outcome measures included device costs, training costs for personnel to use the device, human capital costs of locomotor training, device demand, and the number of training sessions per person with SCI. The perspective of the analysis is from the rehabilitation facilities, specifically Inpatient Rehabilitation Facilities and Long Term Care Hospitals, as the purchasers of technology. A retrospective pre-post study design was implemented to estimate the treatment cost of locomotor strategies. The budget impact of RT-exo was evaluated over one year. Four SCI Model Systems agreed to collaborate on this project: [1] The Shirley Ryan AbilityLab (formerly the Rehabilitation Institute of Chicago), [2]		Not mentioned	Robotic exoskeleton overground training + locomotor training	Conventional overground training		• Table 2 reports BIA inputs and key assumptions concerning the device costs, training costs, and human capital costs associated with locomotor training in inpatient rehabilitation facilities. Where facilities provided more specific data for the analysis, we adapted the inputs accordingly. The duration of all training sessions was assumed to be one hour, including set-up time. We assumed all devices had an adoption rate of 50% across clinicians (i.e., the robotic device sits idle 50% of the time). The adoption rate represents the rate at which the new technology is accepted and the demand for the locomotor training device. We are using assumptions for training session time and adoption rate because RT-exo currently is not used for treatment across facilities. • Table 3 reports the changes in locomotor training strategies between the current and future market share of locomotor strategies within the respective hospital systems. The Appendix provides greater detail of BIA inputs with costs in 2017 USD. • In the base case scenario for all hospital systems, offering RT-exo for locomotor training decreased hospital costs associated with delivering locomotor training (Tables 3 & 4). Providing RT-Exo for 10% of locomotor training sessions over the course of the year results in decreased annual costs associated with locomotor training; these savings ranged from $649 (Facility D) to $4784 (Facility B) per annum. The base case scenario had RT-Exo replacing a combination of all currently used robotic services, treadmill training with body-weight support, and over-ground training. It also assumed that RT-Exo was idle 50% of the time. • The base case scenario was sensitive to several parameters, such as the cost of a robotic exoskeleton, efficiency of robotic exoskeleton use, training strategy substituted, and exoskeleton device life. Fig. 3 plots a series of one-way sensitivity analyses showing the range of costs or savings associated with a change in parameters across each facility. The greatest savings were seen in Facility B ($14,704) where robotic exoskeleton life was extended to 8 years, and the greatest cost was seen in Facility B ($52,934) where robotic exoskeleton adoption rate was limited to 10%. The probabilistic sensitivity analysis simultaneously considered parameter uncertainty of human capital costs (salary), device cost, and locomotor training device substitution. The probabilistic sensitivity analysis produced a range of net budget impacts across facilities from a net savings of $1247per annum in facility C to a net cost of $1620 per annum in facility D. • We explored additional scenario analyses where, instead of choosing to introduce RT-exo, we shift market share to each of the conventional locomotor training strategies by 10%, e.g., in Facility A we assess how locomotor training costs change after we shift from 33 to 43% BWSTT. When stationary robotic and BWSTT are each increased by 10% locomotor training costs increase at all facilities. This is because of the higher personnel cost in BWSTT and higher device cost of stationary robotics relative to the overground training cost. When conventional over-ground training is increased by 10% it lowers costs at all	

Evidence Table : Budget impact analysis (Spinal cord injury)
Question : What is the budget impact of lower limb exoskeleton on gait therapy?

Bibliographic citation	Study Type / Methodology	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
	Craig Hospital, [3] Shepherd Center, and [4] TIRR Memorial Hermann. Participating model system sites served as the primary data source for estimates of resource utilization.						facilities. Full scenario analyses are presented in Appendix 3. For all facilities, the savings from increasing market share to conventional overground training are greater than the savings from shifting market share to RT-exo.	

Evidence Table : Efficacy (Multiple sclerosis) – balance, gait distance, motor function, thalamocortical RSFC
Question : What is the effectiveness of lower limb exoskeleton on gait therapy?

Bibliographic citation	Study Type / Methodology	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
16. Androwis GJ, Sandroff BM, Niewrzol P et al. A Pilot Randomised Controlled Trial of Robotic Exoskeleton-assisted Exercise Rehabilitation in Multiple Sclerosis. Multiple Sclerosis and Related Disorders. 2021; 51: 102936. United States	**Randomised Controlled Trial** **Objective:** To study the effects of 4-weeks of REAER compared with 4-weeks of CGT on functional mobility, walking endurance, CPS, and thalamocortical RSFC outcomes in 10 persons with substantial MS disability. **Method:** Participants were recruited directly from Kessler Institute for Rehabilitation, referrals made by patients' clinician, and a database of previous research participants. Participants underwent initial telephone screening to confirm age between 18-75 years, a neurologist-confirmed definitive MS diagnosis, being relapse-free for 30 days, and seizure-free for 90 days. The experimental condition (REAER) involved 4-weeks of supervised and progressive walking training over-ground in the RE (Ekso-GT, Ekso Bionics, Berkley, CA, USA). The REAER intervention itself took place 2 times/week over 4-weeks on a level surface, and led by a licensed PT. The supervised REAER sessions were individualized, but progressed based on training duration and reliance on robotic assistance.	I	10 patients Intervention (n=6), control (n=4)	Robotic exoskeleton training	Conventional gait training		**Effectiveness** Balance (TUG) There was a non-significant time × group interaction on TUG performance ($F(1,8)=4.92$, $p=.06$, $\eta p^2=0.38$. Although non-significant, the interaction was associated with a large effect (Cohen, 1988), whereby the REAER group demonstrated substantial improvements in TUG performance relative to minimal change in TUG performance for the CGT group (d=-1.20). There further were non-significant main effects of time and group on TUG performance. Gait distance (6MWT) There was no significant difference in follow-up 6MWT performance after controlling for baseline scores. Although the REAER group demonstrated improved 6MWT distance compared with minimal change for the CGT group (d=0.80), this effect was likely due to differences in baseline 6MWT performance. Motor function (SDMT) There was a statistically significant time × group interaction on SDMT scores ($F(1,8)=9.15$, $p=0.02$, $\eta p^2=0.53$); this interaction was large in magnitude based on effect size estimates (Cohen, 1988). Persons who underwent REAER demonstrated substantial improvements in SDMT performance (i.e., 9.2 points) relative to substantial worsening for those who underwent CGT (i.e., 4.5 points) (d=1.42). There further were no other significant effects. Thalamocortical RSFC • There was a statistically significant time × group interaction on RSFC between the thalamus and ventromedial prefrontal cortex ($F(1,8)=20.15$, $p<0.01$, $\eta p^2=0.72$); this interaction was large in magnitude based on effect size estimates (Cohen, 1988). Persons who underwent REAER demonstrated increases in thalamocortical RSFC compared with substantial decreases in RSFC for those who underwent CGT(d=1.64) (see Fig. 4). There were no other significant effects. • Although non-statistically significant, changes in RSFC were moderately associated with changes in TUG, 6MWT, and SDMT performance, respectively, based on effect size estimates (Cohen, 1988), whereby increased thalamocortical RSFC was associated with improved functional mobility, walking endurance, and CPS. These were not statistically significant, likely due to the small sample size. Interestingly, improvement in TUG performance was significantly associated with improvement in SDMT performance whereby reduced time to complete the TUG was associated with increases in SDMT scores from baseline to follow-up; the magnitude of this association was large based on effect size estimates (Cohen, 1988).	

Evidence Table : Efficacy and safety (Multiple sclerosis) – independence level, balance
Question : What is the effectiveness and safety of lower limb exoskeleton on gait therapy?

Bibliographic citation	Study Type / Methodology	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
17. Russo M, Dattola V, De Cola MC et al. The Role of Robotic Gait Training Coupled with Virtual Reality in Boosting the Rehabilitative Outcomes in Patients with Multiple Sclerosis. IJRR. 2018; 0(0). Italy	**Randomised Controlled Trial** **Objective:** To investigate whether an intensive robotic gait training, preceding a traditional rehabilitative treatment, could be useful in improving and potentiating motor performance in MS patients. **Method:** The EG underwent a 6-week robotic training (60 min three time/week) by means of Lokomat-Pro (Hokoma, Switzerland) before 12 weeks of traditional training (60 min three time/week). The CG underwent 18 weeks of traditional rehabilitation training. The standard physical treatment program included general conditioning exercises (i.e. 5 min of warming up; 15 min of lower and upper extremity strengthening; and 40 min of gait and postural control exercise).	I	45 patients (mean ±SD age: 42±7 years; 66.6% females) Intervention (n=30), control (n=15)	Robot-assisted gait rehabilitation + virtual reality + traditional rehabilitation training	Traditional rehabilitation training		**Effectiveness** <u>Independence level (FIM), balance (TBS and TUG)</u> The post-hoc analysis results on FIM and TBS, and TUG are reported. The estimate expressed in the first column of the table represents the mean changes between groups/times. From T0 to T1, a significant improvement for the EG patients was observed for all the outcomes, whereas the CG patients showed an improvement only in TUG. In contrast, from T1 to T2, only CG significantly improved in all outcomes, whereas the EG had an improvement only regarding TUG. From T2 to T3, no significant differences in FIM scores emerged for both groups, but a significant worsening in TBS and TUG was observed for CG patients as well as in TUG for EG patients. **Safety** No patients had any side effects and all the patients completed the study.	

Evidence Table : Cost-effectiveness analysis (Spinal cord injury)
Question : What is the cost-effectiveness analysis of lower limb exoskeleton on gait therapy?

Bibliographic citation	Study Type / Methodology	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
18. Pinto D, Heinemann AW, Chang SH et al. Cost-effectiveness Analysis of Overground Robotic Training Versus Conventional Locomotor Training in People with Spinal Cord Injury. Journal of NeuroEngineering and Rehabilitation. 2023; 20(10). United States	**Cost-effectiveness Analysis** **Objective:** To estimate the cost-effectiveness of locomotor training strategies following spinal cord injury (overground robotic locomotor training versus conventional locomotor training) by injury status (complete versus incomplete) using a practice-based cohort. **Method:** A probabilistic cost-effectiveness analysis was conducted using a prospective, practice-based cohort from four participating Spinal Cord Injury Model System sites. Conventional locomotor training strategies (conventional training) were compared to overground robotic locomotor training (overground robotic training). Conventional locomotor training included treadmill-based training with body weight support, overground training, and stationary robotic systems. The outcome measures included the calculation of quality adjusted life years (QALYs) using the EQ-5D and therapy costs. We estimate cost-effectiveness using the incremental cost utility ratio and present results on the cost-effectiveness plane and on cost-effectiveness acceptability curves. SCI Model Systems are funded by the National Institute on Disability, Independent Living, and Rehabilitation Research (NIDILRR), Administration for Community Living, U.S. Department of Health and Human Services, to support innovation and research in the delivery, demonstration, and evaluation of medical, rehabilitation, vocational, and other health services that meet the needs of people with SCI. Four SCI Model Systems agreed to collaborate on a prospective, longitudinal implementation study to estimate the cost and consequences of locomotor strategies in persons with SCI: (1) The Shirley Ryan			Overground robotic locomotor training	Conventional locomotor training		Quality of life and costs On average, both the conventional training and overground robotic training groups reported QALY improvements as measured by EQ-5D Incremental QALY gains were lower and costs were higher for overground robotic training than for conventional training strategies. When results were analyzed by injury severity, a different pattern emerged. Table 2 reports disaggregated costs and effects for locomotor training strategy by injury severity. Conventional training resulted in QALY improvements for people with incomplete SCI but not for those with complete SCI. Conversely, overground robotic training resulted in QALY improvements for people with complete SCI but not for those with incomplete SCI. Costs were higher for people with complete versus incomplete SCI. Overground robotic training for those with complete SCI had the highest rehabilitation costs, but was also associated with the largest QALY gains. Cost-effectiveness Our probabilistic CEA produced 1000 simulations to characterize uncertainty of cost and effect parameters in the model. Only conventional training for people with incomplete SCI and overground robotic training for people with complete SCI were estimated to produce a positive net benefit. The cost-effectiveness results are plotted on both the cost-effectiveness plane and presented as cost-effectiveness acceptability curves (Figs. 1 and 2). i. Incomplete SCI The majority of cost-effectiveness estimates of conventional strategies for people with incomplete SCI (43%) fall in the right upper quadrant (more effective and more cost), whereas 50% of estimates fall in the left upper quadrant (less effect and more cost) for overground robotic training (Fig. 1A). Conventional training dominated overground robotic training, i.e., it was both more effective and cost less on average. At no level of WTP for an additional QALY was overground robotic training the most cost-effective strategy (Fig. 2A). ii. Complete SCI Locomotor strategies for people with complete injury show a pattern in the opposite direction (Figs. 1B and 2B). The majority of cost-effectiveness estimates for conventional strategies (52%) fall in the left upper quadrant (less effective and more cost), whereas 65% of estimates for overground robotic training fall in the right upper quadrant (more effective and more cost). With low values of WTP for an additional QALY (<$10,000 USD), conventional locomotor strategies are most cost-effective, however at WTP values greater than $10,000 USD per QALY, overground robotic training showed the greatest probability of cost-effectiveness. When comparing locomotor strategies in people with complete SCI, 75% of simulations showed robotic locomotor training to have the greatest net benefit.	

Evidence Table : Cost-effectiveness analysis (Spinal cord injury)
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	AbilityLab (formerly the Rehabilitation Institute of Chicago), (2) Craig Hospital, (3) Shepherd Center, and (4) TIRR Memorial Hermann. Participating Model System sites served as the primary data source for estimates of health-related quality of life and resource utilization in outpatient and community settings. Net benefit was calculated as (50,000 * ΔQALYs) − Δcosts, where $50,000USD represents a conservative threshold for society's willingness to pay (WTP) for an additional QALY. Costs are in 2020 United States dollars (USD) and reflect the healthcare perspective, i.e., the costs considered are those that are relevant to decisions made at the level of the health system.							

Evidence Table : Cost-effectiveness analysis (Hip fracture)
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19. Manetti S, Turchetti G and Fusco F. Determining the Cost-effectiveness Requirements of an Exoskeleton Preventing Second Hip Fractures Using Value of Information. BMC Health Service Research. 2020; 20: 955. United Kingdom	**Cost-effectiveness Study** **Objective:** Not mentioned. **Method:** We performed an early cost-effectiveness analysis of a robotic exoskeleton, by simulating its use both in a care home and in patients' home settings, in addition to UK standard post-hip fracture care. Our analyses are based on a previously published Markov model developed in Excel (Microsoft, Redmond, WA). The model described the natural history of patients with hip fractures and, by doing so, estimated the life-expectancy trajectories, allowing us to calculate the lifetime costs and Quality Adjusted Life Years (QALYs) of the simulated patients. These estimates were conditional on health states reflecting the natural history of hip fracture: history of primary hip fracture, second hip fracture and major non-hip fractures (e.g. wrist, spine, humerus) necessitating hospitalisation. These states were implemented both in a care-home and own home settings. Death was modelled as 30-day mortality after a fracture or within a year. Once patients were moved to a care-home, they were not modelled to return to their own home. The cycle length used was one year, applying a half-cycle correction. A 3.5% annual discount rate was applied to costs (2012/2013 UK sterling) and to QALYs.		The population simulated in our model reflects the of the UK population who had experienced a hip fracture observed between 2003 and 2013. Our analyses focused on high-risk subpopulations and included patients with dementia and patients with CVD (i.e. stroke, myocardial infarction). The subgroups explored in our analyses were sex and age specific risks at 65, 75 and 85 years old.	Robotic exoskeleton	NI		<u>Base-case</u> The Markov model simulated cohorts of 1000 patients to reflect the characteristics of dementia and CVD patients accessing a hospital because of a hip fracture in the UK. Our model showed that the exoskeleton could lead to a substantial increment of QALYs regardless of patients' age and comorbidities. For patients with CVD, the exoskeleton is estimated to be cost-effective only in CVD patients younger than 75 years (ICER (female): £18,753; ICER (male): £19,598). For dementia patients, the exoskeleton is similarly cost-effective in preventing SHF only in individuals not older than 75 years. The ICER for dementia patients ranged from £18, 083 (65-year-old female) to £19,900 (75-year-old male). The 95% CIs of the HR and HRQOL utility-ratio ranged from 0.60 to 0.94 and from 1.46 to 1.93, respectively. As a result of these uncertainties, the population EVPI of cost-effective scenarios for female patients ranged from £12,058,172 (CVD - 65 years old) to £29, 986,626 (dementia - 75 years old), whilst the population EVPI for 65-year-old women with dementia was £20, 332,551. The smaller proportion of male patients experiencing a hip fracture, approximately 25% of the HES extract, was reflected by the population EVPI, which ranged from £5,275,225 (CVD - 65 years old) to £9,920,712 (dementia - 75 years old). The population EVPI for male patients aged 65 with dementia was £5, 460,316. <u>Leasing</u> The importance of HRQOL across the leasing scenarios is more prominent than fall prevention (Fig. 2; panels a and b). The exoskeleton was not cost-effective unless it provided a gain in patients' HRQOL by 25% paired to a HR of falling of 0.625. However, the reduction in the number of second hip fractures was not a limiting factor for cost-effectiveness, especially in less expensive scenarios. The largest HR of falling that still ensured the device's cost-effectiveness was 1.125, however, this scenario needs to be paired with a larger increment in HRQOL, namely 30%. Conversely, the prevention of hip fractures had a relevant impact in scenarios simulating more expensive leasing fees (e.g. £6000 annual leasing). These fees could be justified only if the exoskeleton was not inferior to usual care, and would provide on average a larger improvement in patients' HRQOL. The proportion of cost-effective scenarios did not materially differ between disease groups, regardless of sex. <u>Purchase</u> Compared to the leasing scenarios, purchasing the device (Fig. 2; panels c and d) was less likely to be a cost-effective alternative. In this respect, the HRQOL influences the results of the purchase scenarios to a smaller extent than it did for the leasing scenarios. Overall, to represent good value for money, the device should provide at least an increment of patients' HRQOL by 48% alongside an HR of falling of 50% SHF. Similarly, to the leasing scenarios, the HR of falling does not influence predominantly the cost-effectiveness of the device (i.e. the threshold value	

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							is 1.25), but the increment in HRQOL will need to be substantially large, namely 57.5%. Selling the device is more likely to be a cost-effective alternative in patients with dementia, especially in women not older than 75 years (Fig. 2; panels c and d).	

TECHNOLOGY REVIEW (MINI HTA) LOWER LIMB EXOSKELETON FOR GAIT THERAPY

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