Online version at http://www.minervamedica.it

European Journal of Physical and Rehabilitation Medicine 2021 October;57(5):831-40
DOI: 10.23736/S1973-9087.21.06922-7

SYSTEMATIC REVIEW

THE ITALIAN CONSENSUS CONFERENCE CICERONE

State of the art and challenges for the classification of studies on electromechanical and robotic devices in neurorehabilitation: a scoping review

Marialuisa GANDOLFI [1] *, Nicola VALÈ [2], Federico POSTERARO [3], Giovanni MORONE [4], Antonella DELL'ORCO [1], Anita BOTTICELLI [1], Eleonora DIMITROVA [2], Elisa GERVASONI [5], Michela GOFFREDO [6], Jacopo ZENZERI [7], Arianna ANTONINI [8], Carla DANIELE [9], Paolo BENANTI [10], Paolo BOLDRINI [11], Donatella BONAIUTI [12], Enrico CASTELLI [13], Francesco DRAICCHIO [14], Vincenzo FALABELLA [15], Silvia GALERI [5], Francesca GIMIGLIANO [16], Mauro GRIGIONI [17], Stefano MAZZON [18], Franco MOLTENI [19], Maurizio PETRARCA [20], Alessandro PICELLI [1], Michele SENATORE [21], Giuseppe TURCHETTI [22], Daniele GIANSANTI [23], Stefano MAZZOLENI [24]
on behalf of the Italian Consensus Conference on Robotics in Neurorehabilitation (CICERONE)‡

[1]Unit of Neurorehabilitation, Department of Neuroscience, Biomedicine, and Movement Sciences, University Hospital of Verona, University of Verona, Verona, Italy; [2]Department of Neuroscience, Biomedicine and Movement Sciences, University of Verona, Verona, Italy; [3]Department of Rehabilitation, Hospital of Versilia, ASL Toscana Nord-Ovest, Lucca, Italy; [4]IRCCS Santa Lucia Foundation, Rome, Italy; [5]IRRCS Fondazione Don Carlo Gnocchi, Milan, Italy; [6]Department of Neurological and Rehabilitation Sciences, Neurorehabilitation Research Laboratory, IRCCS San Raffaele Pisana, Rome, Italy; [7]Department of Robotics, Brain and Cognitive Sciences, Istituto Italiano di Tecnologia (IIT), Genoa, Italy; [8]AITO Umbria, Perugia, Italy; [9]Istituto Superiore di Sanità, Rome, Italy; [10]Pontifical Gregorian University, Rome, Italy; [11]Italian Society of Physical Medicine and Rehabilitation (SIMFER), Rome, Italy; [12]Geriatric Institute Piero Redaelli, Milan, Italy; [13]Pediatric Neurorehabilitation, Bambino Gesù Children's Hospital, Rome, Italy; [14]Department of Occupational and Environmental Medicine, Epidemiology and Hygiene, INAIL, Rome, Italy; [15]Italian Federation of Persons with Spinal Cord Injuries (Flip Onlus), Rome, Italy; [16]Department of Mental and Physical Health and Preventive Medicine, Luigi Vanvitelli University of Campania, Naples, Italy; [17]National Center for Innovative Technologies in Public Health, Italian National Institute of Health, Rome, Italy; [18]ULSS 6 (Unique Sanitary Local Company) Euganea Padova – Distretto 4 "Alta Padovana," Padua, Italy; [19]Villa Beretta, Costa Masnaga, Como, Italy; [20]The Movement Analysis and Robotics Laboratory, Bambino Gesù Children's Hospital, Rome, Italy; [21]Italian Association of Occupational Therapists (AITO), Rome, Italy; [22]Institute of Management, Scuola Superiore Sant'Anna, Pisa, Italy; [23]National Center for Innovative Technologies in Public Health, Italian National Institute of Health, Rome, Italy; [24]Department of Electrical and Information Engineering, Polytechnic of Bari, Bari, Italy

‡Members are listed at the end of the paper

*Corresponding author: Marialuisa Gandolfi, Unit of Neurorehabilitation, Department of Neuroscience, Biomedicine, and Movement Sciences, University Hospital of Verona, University of Verona, Piazzale LA Scuro 10, 37134 Verona, Italy. E-mail: marialuisa.gandolfi@univr.it

ABSTRACT

INTRODUCTION: The rapid development of electromechanical and robotic devices has profoundly influenced neurorehabilitation. Growth in the scientific and technological aspects thereof is crucial for increasing the number of newly developed devices, and clinicians have welcomed such growth with enthusiasm. Nevertheless, improving the standard for the reporting clinical, technical, and normative aspects of such electromechanical and robotic devices remains an unmet need in neurorehabilitation. Accordingly, this study aimed to analyze the existing literature on electromechanical and robotic devices used in neurorehabilitation, considering the current clinical, technical, and regulatory classification systems.

EVIDENCE ACQUISITION: Within the CICERONE Consensus Conference framework, studies on electromechanical and robotic devices used

for upper- and lower-limb rehabilitation in persons with neurological disabilities in adulthood and childhood were reviewed. We have conducted a literature search using the following databases: MEDLINE, Cochrane Library, PeDro, Institute of Electrical and Electronics Engineers, Science Direct, and Google Scholar. Clinical, technical, and regulatory classification systems were applied to collect information on the electromechanical and robotic devices. The study designs and populations were investigated.

EVIDENCE SYNTHESIS: Overall, 316 studies were included in the analysis. More than half (52%) of the studies were randomised controlled trials (RCTs). The population investigated the most suffered from strokes, followed by spinal cord injuries, multiple sclerosis, cerebral palsy, and traumatic brain injuries. In total, 100 devices were described; of these, 19% were certified with the CE mark. Overall, the main type of device was an exoskeleton. However, end-effector devices were primarily used for the upper limbs, whereas exoskeletons were used for the lower limbs (for both children and adults).

CONCLUSIONS: The current literature on robotic neurorehabilitation lacks detailed information regarding the technical characteristics of the devices used. This affects the understanding of the possible mechanisms underlying recovery. Unfortunately, many electromechanical and robotic devices are not provided with CE marks, strongly hindering the research on the clinical outcomes of rehabilitation treatments based on these devices. A more significant effort is needed to improve the description of the robotic devices used in neurorehabilitation in terms of the technical and functional details, along with high-quality RCT studies.

(*Cite this article as*: Gandolfi M, Valè N, Posteraro F, Morone G, Dell'Orco A, Botticelli A, *et al*.; Italian Consensus Conference on Robotics in Neurorehabilitation (CICERONE). State of the art and challenges for the classification of studies on electromechanical and robotic devices in neurorehabilitation: a scoping review. Eur J Phys Rehabil Med 2021;57:831-40. DOI: 10.23736/S1973-9087.21.06922-7)

KEY WORDS: Nervous system diseases; Upper extremity; Lower extremity; Gait; Rehabilitation; Robotics.

Introduction

Over the past two decades, neurorehabilitation has undergone profound changes owing to advances in technology, and specifically owing to the diffusion of electromechanical devices and robots into clinical settings.[1-4] Growth in the scientific and technological aspects thereof is crucial for increasing the number of newly developed devices, and clinicians have welcomed such growth with enthusiasm.[5, 6]

Three main perspectives can be used to classify the electromechanical and robotic devices used in neurorehabilitation: clinical, technical, and regulatory.

From a clinical perspective, a robotic device is a vehicle providing intensive, repetitive, and task-oriented treatments.[6, 7] Although there is a lack of convincing evidence to support the superiority of one approach over the others,[8-10] treatments focusing on these three elements (high-intensity, repetition, and task-oriented practice) have shown encouraging results regarding improving motor function and recovery.[10] Furthermore, outcomes can be further improved by driving neuroplasticity phenomena, *e.g.*, by increasing the treatment complexity (*i.e.*, perturbative, assistive) and providing multimodal feedback in a motivating environment, with an increased attentional load.[11, 12] The use of robotic devices can address these determinant characteristics.[13] However, the mere use of a robotic device is not sufficient for fully specifying the features and effects of these treatments. The simple application of these devices for providing standardized and repetitive training does not use their full therapeutic potential. Human-robot interaction modalities have been described in literature from, for instance, 'assisted therapy' where the robot is active and the user is passive, to 'perturbative modality', where the robot randomly applies disturbances (in terms of applied forces or velocities) during the execution of a task.[13] Moreover, the modalities of robot-assisted rehabilitation include the definition of the environment (real or virtual reality-based), difficulty level of the tasks (variable or fixed), and possibility of adapting kinematic and force parameters to the treatment. The existing literature has often overlooked systematic reporting on the types of exercises, modalities of execution,[14] and features of the device used during rehabilitation. In general, the results are based on comparing the effects of robot-assisted *versus* non-robotic interventions.[3, 15, 16]

A recent review by Morone *et al*.[5] highlighted the need to report and investigate the specific features maximizing the effects of robot-assisted upper-limb rehabilitation. Although there are common and essential elements that can characterize robotic devices for neurorehabilitation, the devices differ regarding several factors and functional modalities. Moreover, the interpretation of clinical effects is often not linked to specific knowledge regarding the device(s).[17]

From a technical point of view, the definition of the term 'robot' is a non-trivial question. A robot is an electromechanical device equipped with actuators, a sensor system, and a control system.[18] The ability to mobilize limbs, whether in the context of locomotion or manipulation, is provided by the actuators, which move the robot's mechanical components in contact with the human body parts (*i.e.*, arms and legs). Sensors acquire data on the internal state of the mechanical system (*e.g.*, proprioception sensors and position transducers) and the environment's external state (*e.g.*, exteroceptive sensors and force sensors), facilitating user

interactions. The control system links actions to perceptions through different control strategies (*i.e.*, admittance and impedance). From a mechanical perspective, robots can be classified into exoskeletons and end-effector systems, and/or according to the control system. Exoskeleton-based systems are robots for performing the same type of movement performed by the patient (*i.e.*, joints on the mechanical structure are aligned with human joints). The human-machine mechanical interface is extended to the entire limb (or part of it). Consequently, robot joints are designed to reproduce human-like movements compatible with the natural motions of human joints. In contrast, in end-effector systems, the contact between the mechanical structure and patient is limited to the most distal segment of the involved limb (*i.e.*, hand/foot). Moreover, some systems are limited to planar or mono-dimensional movements, whereas others support the exploration of the entire three-dimensional space. The control systems implemented in these devices can be mainly divided into 'impedance' and 'admittance' control, although other types of control techniques can be used (*e.g.*, position control, force control).

The European regulatory framework requires a robotic device to be registered as a medical device and provided with the CE mark before being placed in the European Union market. The normative document that defines CE registration ensures the fulfilment of European standards regarding quality and safety. Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices (amending Directive 2001/83/EC, Regulation (EC) No 178/2002, Regulation (EC) No 1223/2009, and repealing Council Directives 90/385/EEC and 93/42/EEC) is a policy document for defining the criteria for the classification of medical devices according to their intended use.[19] Regulation (EU) 2017/745 on medical devices was entered into force on 25 May 2017. Owing to the COVID-19 outbreak, the Regulation (EU) 2020/561 of 23 April 2020 was deferred by one year to 26 May 2021, *i.e.*, the full application of the 'Medical Device Regulation' (MDR).

The MDR promotes a shift from preapproval to a life-cycle approach. Risk management and the connected processes of postmarket surveillance and clinical evaluation are required to be conducted continuously throughout a product's life cycle.

Compared to previous regulations, some classification rules are new or have been amended, whereas others remain unchanged. The MDR brings stronger supervision of the notified bodies by national authorities, and economic operators' roles (*i.e.*, manufacturer, authorized representative, distributor, importer) are narrowly defined. Each economic operator must ensure that their corresponding role is fully understood, and agreements are set up accordingly. Finally, manufacturers are suggested to consider generating clinical data to provide sufficient clinical evidence.

As regards the US market, FDA's Center for Devices and Radiological Health (CDRH) is responsible for regulating firms who manufacture, repackage, relabel, and/or import medical devices sold in the United States. Medical devices are classified into Class I, II, and III. Regulatory control increases from Class I to Class III. The device classification regulation defines the regulatory requirements for a general device type.[20]

In our view, clinicians should be aware of each of these three perspectives (clinical, technical, and regulatory). First, a clinical standpoint is essential for allowing replication, and for explaining the effects of robot-assisted rehabilitation treatments. Second, reporting on the technical features of the main devices is crucial for the effective and appropriate use of robots when introduced in a clinical setting. Finally, considering the regulatory background and market availability allows for a safe application of the device in clinical settings.

To date, an overall integrated view of reporting clinical, technical, and regulatory aspects remains lacking, as clinical studies have generally not provided descriptions of the devices used, or the corresponding treatment modalities. The studies have mainly focused on the technical aspects of the devices, and it is difficult to translate this information into clinical practice. Accordingly, the inclusion of the above-mentioned determinants may contribute to the development of the field.

Within the CICERONE Consensus Conference framework, this study aimed to provide an overview on the electromechanical and robotic devices used in neurorehabilitation, considering the current clinical, technical, and regulatory classification systems. This review suggests a set of fundamental information to be reported in studies on electromechanical and robotic devices in a multifactorial classification system integrating the relevant clinical, technical, and European regulatory frameworks. In comparison to the other existing systematic reviews on this topic, we have not proposed a critically appraised and synthesized result to a question addressing the feasibility, appropriateness, meaningfulness, or effectiveness of a particular treatment or practice, for which a systematic review represents the correct approach. This work also promotes and supports close interactions between developers/designers and clinical users.

Evidence acquisition

Eligibility criteria

In this study, a literature review was conducted. According to the CICERONE Consensus Conference framework, the selected studies considered robot-assisted rehabilitation for subjects affected by neurological diseases. The definition proposed by Siciliano *et al*.[18] was used to identify robotic devices. Patients with acquired and congenital neurological conditions such as strokes, traumatic brain injury (TBI), multiple sclerosis (MS), Parkinson's disease (PD), spinal cord injury (SCI), and cerebral palsy (CP) were included, considering both the acute and chronic stages of the disease. Only English-written clinical trials, pilot studies, and observational studies were considered. Clinical studies combining robot-assisted approaches with other non-invasive technologies (*e.g.*, non-invasive brain stimulation and functional electrical stimulation) were excluded.

Information sources

We conducted a literature search from November 2019 to January 2020. Three authors independently and synchronously searched the following databases: MEDLINE, Cochrane Library, PeDro, Institute of Electrical and Electronics Engineers, Science Direct, and Google Scholar.

Search

Several search strategies were used, as indicated below:

- "keywords" AND robot OR exoskeleton OR end-effector OR robotics OR exoskeleton device AND upper limb OR upper extremity OR arm OR hand AND function OR rehabilitation OR recovery. "Keywords" referred to the pathologies included in the study, *e.g.,* cerebral stroke, head trauma, SCI, MS, PD, and ataxia;
- "keywords" AND (robotics [mh] OR robot-assisted OR Electric Stimulation Therapy/instrumentation "[mh] OR electromechanical) and (rehabilitation [mh] OR training) and (postural balance [mh] OR gait);
- (pediatric OR child *) AND robot * AND (rehabilitation) AND ('Lower Extremity '[Mesh] OR balance);
- (pediatric OR child *) AND robot OR exoskeleton OR end-effector OR robotics OR exoskeleton device AND upper limb OR upper extremity OR arm OR hand AND function OR rehabilitation OR recovery.

Six authors in each group independently reviewed the literature for each topic and assessed the inclusion criteria to extract relevant information.

Data collection

The working group was divided into three subgroups, each with a specific field of application: devices for the upper limbs in adult patients (Subgroup 1), devices for walking and balance in adult patients (Subgroup 2), and devices for rehabilitation at developmental age (Subgroup 3). For each article, the data collection form included three subsections, referring to the clinical, technical, and regulatory aspects, respectively (Table I).

The first information subsection referred to the clinical features, including the study authors, clinical characteristics of the population, study design, and rehabilitation aim(s).

The second subsection referred to technical features, such as a compliance check with the definition of a robotic or electromechanical device,[18] type of device (end-effector or exoskeleton), wearability, body district involved, environment of the intervention (virtual or real), modalities of

TABLE I.—*Overview of the clinical, technical, and regulatory aspects to be included in the proposed classification.*

	Study authors
Clinical	Clinical characteristics of the population
	Patients [ST, TBI, MS, PD, SCI, CP]
	Time since disease onset [≥6 months, <6 months]
	Study Design [Observational, Pilot multicenter, Pilot, randomized controlled trial (RCT), Controlled Prospective, Case series, Uncontrolled trial, Feasibility study]
	Rehabilitation aim [Assistive/Interactive]
Technical	M.o.I. [Active, Passive]
	Robot/Electromechanical
	EE/Exo
	Wearability [0, 1]
	Environment [Real, Virtual]
	Assistance modality [0,1,2,3,4,5,6,7]
	Feedback [0,1,2,3]
	DoFs [nActive + nPassive]
	Body segment [0, 1, 2, 3, 4, 5, 6, 7, 8, Lower limb]
	Difficulty level [Fixed, Adjustable]
	Recorded parameters [ROM, Force, Kinematics]
	Control system [Force, ROM, Impedance, EMG]
	Movement dimension [2D/3D]
Regulatory	CE class [I, IIa, IIb]
	CE mark [Yes/No]
	Market [Yes, No]
	Devices National Classification according to the Italian regulatory system [code].

Numbers in brackets indicate different characteristics: body segment (0: whole upper limb; 1: shoulder/elbow; 2: shoulder/elbow/wrist; 3: elbow/wrist/hand; 4: elbow/wrist; 5: elbow; 6: wrist; 7: wrist/hand; 8: hand); Wearability (0: no, 1:yes); assistance modality (0: passive; 1: active; 2: assistive; 3: active assisted; 4: passive-mirrored; 5: corrective; 6: path guidance; 7: resistive), feedback (0: none; 1: visual; 2: auditory; 3: haptic).
ST: stroke; TBI: traumatic brain injury; MS: multiple sclerosis; PD: Parkinson's disease; SCI: spinal cord injury; CP: cerebral palsy; M.o.I.: Modality of Interaction: EE: end-effector; Exo: exoskeleton-based; DoFs: degrees of freedom; n: number; ROM: range of motion; EMG: electromyography.

the human-robot interactions,[14] type of feedback provided to the user, degrees of freedom for each limb, number of spatial dimensions of movement, possibility of adapting the level of training difficulty, parameters recorded by the device, and control system.

The third subsection addressed regulatory aspects, such as the use according to EU regulation 2017/745, the CE mark and relative classification if available, and commercial availability.[19]

Evidence synthesis

Overall, 316 studies were included and analyzed (Table II). More than half (52%) of the studies were randomized controlled trials (RCTs). The most investigated population was that affected by strokes, followed by SCI, MS, CP, and TBI. In total, 100 devices were described; of these, 19% were certified with a CE mark. Overall, the main type of device was an exoskeleton. However, end-effector devices were primarily used for the upper limbs, whereas exoskeletons were used for the lower limbs in both childhood and adults (Figure 1A, B).

Studies in adult patients

Most of the studies investigated walking and balance (N.=164), rather than upper-limb rehabilitation (N.=99). In both cases, most of the studies were RCTs (63% and 53%, respectively). The most-surveyed population was

TABLE II.—*Overview of the included studies.*

	Total	Study design		Population*	Devices°	CE mark°	EE/Exo°
		RCT	Other	ST/TBI/MS/PD/SCI/CP			
	N. (%)	N. (%)	N. (%)	N.	N. (%)	N. (%)	N.
All studies	316	164 (52%)	153 (48%)	172/17/21/9/57/45	100	19 (19%)	47/53
Adults							
Upper limb	99 (31%)	52 (53%)	48 (47%)	85/2/7/1/8/0	44	11 (25%)	26/18
Walking and balance	164 (52%)	103 (63%)	61 (37%)	84/3/14/8/48/0	39	7 (18%)	10/29
Childhood							
Upper limb	22 (7%)	2 (9%)	20 (91%)	3/11/0/0/0/16	8	3 (38%)	7/1
Walking and balance	31 (10%)	7 (23%)	24 (77%)	0/1/0/0/1/29	17	3 (18%)	9/8

N.: number; Other: pilot: feasibility: observational studies; ST: stroke; TBI: traumatic brain injury; MS: multiple sclerosis; PD: Parkinson's disease; SCI: spinal cord injury; CP: cerebral palsy; EE: end-effector; Exo: exoskeleton.
*Studies may include more than one population (*i.e.*, stroke and TBI), and devices may be counted in both adult and childhood populations.

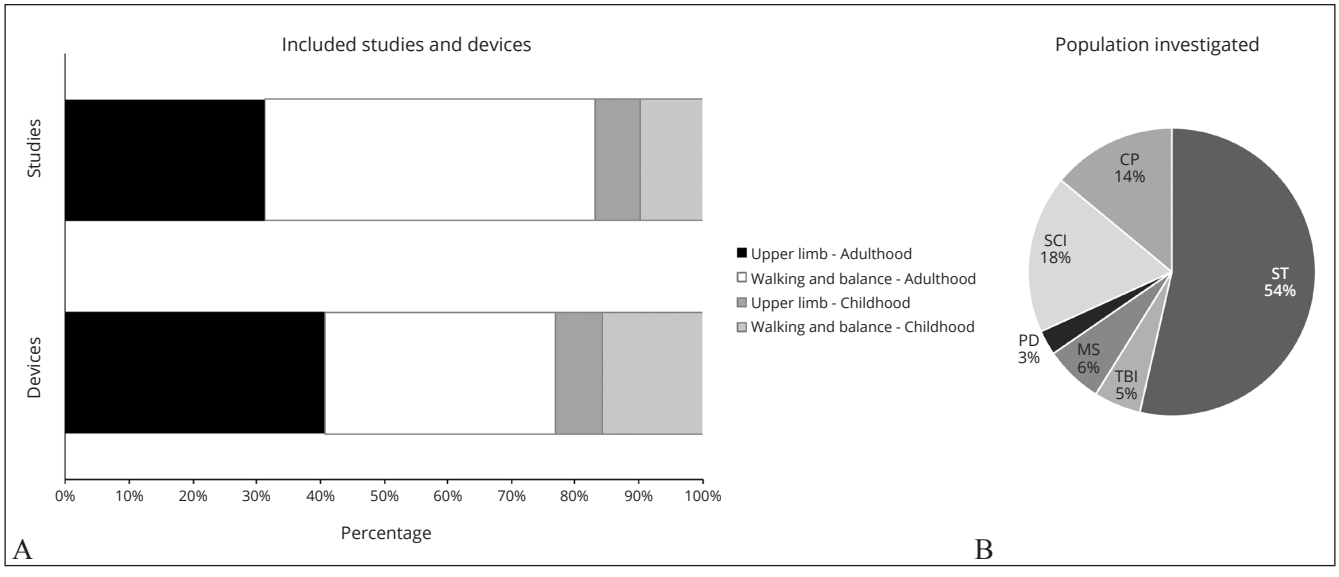

Figure 1.—A) Summary of included studies and devices. B) Summary of population investigated.
ST: stroke; TBI: traumatic brain injury; MS: multiple sclerosis; PD: Parkinson's disease; SCI: spinal cord injury; CP: cerebral palsy.

the stroke population (169 studies), followed by SCIs (56 studies) and MS (21 studies). Patients with PD were mostly investigated in walking and balance rehabilitation studies. In total, 44 types of upper-limb devices were identified; of these, only 11 had the CE mark. For walking and balance rehabilitation, we identified 39 devices; of those, seven were provided with the CE mark.

In walking and balance rehabilitation, a limited number of studies focused on prototypes. In contrast, CE-marked devices (*e.g.*, Lokomat, G-EO System; Rockland, MA, USA) were extensively investigated. Across the studies, the human-machine interaction modalities were generally assistive. The feedback provided to the patients was essentially haptic and, in a few cases, visual. A limited number of studies used multiple modalities. Detailed information on the reviewed studies is reported in Supplementary Digital Material 1 (Supplementary Table I, Supplementary Text File 1).

Studies in childhood

The analysis of the literature on pediatric robot-assisted rehabilitation showed a limited number of studies relative to the number for adults. It is possible that the wide range of subject heights during childhood affects the diffusion of standard devices (in contrast to customized robots). Moreover, the methodological quality and study design quality were lower for children, with only nine RCT studies. The most studied pathology was CP, followed by acquired brain injuries (TBI and stroke), and the ages of the subjects were mainly between 12 and 18 years.

Only eight types of upper-limb devices were identified, of which three were provided with the CE mark. For walking and balance rehabilitation, we identified 17 devices, three with the CE mark. Of the remaining 14 devices, five were custom-made prototypes. In parallel with adult patients' devices, most of the upper-limb devices were end-effectors, whereas most of the walking and balance devices were exoskeletons.

Overall, there were no devices able to actively mobilize all the joints of the upper limbs (shoulder, elbow, wrist, and hand); in fact, most of them were only able to mobilize the proximal districts (shoulder and elbow), some systems were found to be specific to the wrist, and only a few were specifically designed for hand rehabilitation. As for the assistance modality and user feedback, the various devices could be considered as relatively homogeneous (assistive), with both visual and haptic feedback. Detailed information on the reviewed studies is reported in Supplementary Digital Material 1.

Discussion

The present review revealed a remarkable number of studies on the robotic devices used in neurorehabilitation. Many robots have been used for upper and lower-limb rehabilitation in adulthood. While most upper-limb devices have been investigated only in a limited number of studies, certain lower-limb devices have been extensively investigated (*e.g.*, Lokomat and G-EO System). Only a few devices, mostly prototypes, have been investigated for subjects of developmental age.

Lack of reporting robot-assisted treatment details

The application of our data collection to the existing literature showed that a relevant number of studies provide only limited details regarding robot-assisted treatment, affecting the possibility of replicating their findings in clinical settings. Moreover, it is generally challenging to obtain detailed information on the devices' descriptions and training modalities; this affects the understanding of the possible neurophysiologic mechanisms that may support the clinical effects.

Robot-assisted therapy intervention is often not adapted to the specific disease

From a clinical perspective, most studies focused on the effects of robot-assisted rehabilitation procedures. However, little emphasis was given to the contents of the treatments and/or the specific exercises provided. This shift of attention mirrored the robotic rehabilitation paradox described by Morasso *et al*.[17] According to this paradox, there is strong evidence that a rehabilitation approach should be highly personalized to be effective. However, in most trials, the robot-assisted interventions are standardized, regardless of the impairment. This standardization could lead to underestimating the effects of a robot-assisted approach and could limit a device's potential disclosure. Moreover, different neurologic pathologies were investigated in the reviewed studies, but the focus on adapting the intervention(s) to specific diseases was relatively narrow. There is compelling evidence that neuroplasticity plays a crucial role in functional recovery from central nervous system focal lesions (*e.g.*, from stroke or TBI) and neurodegenerative diseases (*e.g.*, MS). It is conceivable that different etiologies require different treatment features. For example, high-intensity treatments are needed to improve motor functions and activity in stroke patients, but subjects suffering from MS could benefit from slightly different approaches.[9, 21, 22]

Most of the studies investigated cerebral stroke rehabilitation, with particular focus on patients in the chronic phase of the disease. Research on stroke rehabilitation has historically focused on chronic patients; nevertheless, the literature has also reported that early mobilization and interventions reduces hospitalization length and improves disability.[23, 24] Despite the lack of evidence, it is reasonable that some features of robotic devices, such as the possibility of performing passive or assisted movements, are likely to be relevant to the acute and sub-acute phases of the disease. Therefore, further investigations should be encouraged on implementing robot-assisted rehabilitation in the acute phase.

Association between robots' features and rehabilitation contents

The literature analysis showed a limited understanding of the clinical relevance of robots' main features and their modalities of intervention. Moreover, the neurological underpinnings of robot-assisted recovery are not entirely understood. Although intensive training, which has been reported as essential for driving neuroplasticity, can be performed using robotic devices, the increments in the number of repetitions are not sufficient to stimulate neuroplasticity per se.[25] Little focus has been given to other treatment features, such as the level of assistance or the complexity of the movements performed, and/or their associations with motor recovery. As such, different training modalities should be investigated separately, to adjust the treatment characteristics to the patient's impairments. For instance, while passive or assisted training can represent an optimal choice for most impaired patients, active or perturbated modalities might be adequate for achieving higher motor performance.[5, 14, 26-28] Notably, an active assist-as-needed modality has shown promising results, being engaging, challenging, and adaptive to the patient's ability.[13, 14] Meanwhile, the distal-*versus*-proximal approach for upper-limb robotic training (and its related rehabilitation strategies) remain little explored.[29]

Lack of treatment modalities' reporting

In most studies, the information on the technical aspects of the device was not exhaustive. Clinicians generally reported on the classical distinction between exoskeletons and end-effector types but lacked sufficient details on other relevant device components. For instance, reporting the number of degrees of freedom along with the definitions of training modalities is important for explaining the complexity of the performed movements. This shortcoming could be because the development of the rehabilitation sector has been affected by limited communication between the designers of the devices and final users (*i.e.*, physicians and physiotherapists). Several factors may have played a relevant role in this scenario. First, engineers and developers are pushed by the market and the need for continuous technological innovation, whereas clinicians need time to learn to use and take full advantage of the new devices. This has led to a gap between the development of new devices and the time needed for their integration into clinical practice. Second, while robotic engineers are often focused on technical issues, clinicians mainly focus their attention on the application of such devices and attach less importance to the knowledge of their specific characteristics. Lastly, a certain extent of skepticism regarding technological devices has been reported in clinical settings.[30] Previous studies have suggested that these beliefs originated from the lack of compelling evidence on the effectiveness of robot-assisted rehabilitation, or on the idea that robotic devices could replace the work of clinicians.[30] However, it is well-known that the aim of introducing robotic devices is not to replace health care providers, but to improve their treatment options.[31] Clinician opinions on robot-assisted rehabilitation are crucial for the further development of this scientific and technological field.

Stakeholders' roles in improving research reporting on robot-assisted rehabilitation

The limitation in reporting either on technical features of robotic devices or on rehabilitation protocols used could eventually affect the diffusion of robotic devices in rehabilitation. Moreover, it is conceivable that poor description of robot-assisted intervention could limit the efficacy of robotic devices use in clinical settings. The close and continuous cooperation between developers and clinicians should be supported to overcome these aspects. The researcher's role in this scenario is crucial. Scientific literature could fill the gap between these two approaches (*i.e.*, clinical and technical). Studies can provide robot designers with evidence of the neurophysiologic assumptions underlying effective rehabilitation treatments. This would allow for the design of devices with specific features to improve rehabilitation outcomes. In addition, the literature can provide physicians and physiotherapists with precise information on the functioning of robotic devices, so that they can take full advantage of their features and co-design individualized and effective exercises. In this case, researchers and clinicians would have the opportunity to overcome the Achilles heel of using robotics in neurorehabilitation, *i.e.*,

the lack of translation. Better communication by researchers and developers, and that regarding clinical indications and expectations, could foster the clinician's understanding of the potential impacts of robotic devices on neurorehabilitation, avoiding excessive optimism on the one hand and heated pessimism on the other. Consequently, overcoming these aspects may improve the diffusion of robotic devices, the quality of rehabilitation treatments, and their efficacy. Improving the reporting of technical aspects will also allow the comparison of the effects of different devices and training modalities. However, we must not forget the great steps made in recent years in terms of robotic training variability and increased usability. These steps were made considering the complex and specialized functions acquired by humans through phylogeny over millions of years (upright walking, reaching, and grasping) and the underlying complex neurophysiological phenomena (*e.g.*, motor control and coordination, motor synergies, grasping models, or walking control mechanisms) are not fully understood.[32, 33]

Lack of technological devices regulatory aspects and economics of robotic and electromechanical devices treatments

Remarkably, of the many devices investigated, only a small fraction was provided with CE certification (18/94). Many devices were prototypes, or their production was limited to an investigation site. This leads to a twofold drawback. This limited the reproducibility and generalization of the findings in other settings. The CE registration ensures high quality and safety standards, both essential aspects of patient-centered rehabilitation care. The absence of such certification could, therefore, affect the fulfilment of these required standards. Although the process could be demanding, producers should be encouraged to undergo the process to obtain the CE mark.

This issue is sensitive and the type of analysis that we have conducted does not allow to draw a firm conclusion. However, based on our data, we recommend promoting the technological transfer from applied research to the clinical practice and to the market, when viable and applicable. Prototypes represent important tools able to provide preliminary evidence on technical validation and clinical application of developed devices, but these studies should be followed by higher methodological quality studies (*e.g.*, RCTs) to provide strong evidence on the effectiveness of such interventions. In this context, RCTs may represent relevant milestones in the procedure for obtaining the CE certification thanks to the provided evidence on the device applicability and therapeutic effectiveness in the clinical setting.

Within the framework of the technology transfer above mentioned, the acquisition of the CE certification might include this type of evidence-based path. Indeed, in this review we have reported devices that were investigated in observational studies or in RCTs.

From a national healthcare system perspective, reporting on the regulatory aspects of technological devices and the economics of treatments conducted by robotic and electromechanical devices remains lacking.

Conclusions

In conclusion, we herein have proposed a set of data that should be provided in studies addressing robot-assisted rehabilitation. The integration of information related to the commercial and regulatory domains, technical characteristics of the robots, and provided treatment modalities are essential to improving the quality of the studies and clinical use of the devices. After the first pioneering phase that began at the end of the 1990s, there remains a need to perform more specific studies and increase the methodological quality of such studies to clarify which (and how) robotic devices can improve the recovery of patients affected by neurological diseases. It is necessary for the scientific community to make a more significant effort to improve the description of the electromechanical and robotic devices used in neurorehabilitation and the treatments performed, in terms of the technical and functioning details. This would enhance clinicians' awareness of the specific characteristics of the devices they use in clinical practice. Further investigation is necessary to develop additional feedback and interaction methods, especially for lower-limb devices in the rehabilitation of persons with neurological disorders. Finally, it is necessary to increase the number of clinical studies based on multi-center RCT design (at least single-blind) and with appropriate sample sizes, so as to analyze the effects of the robot type and impairment severity associations, and to define the critical factors of robot-assisted rehabilitation, *i.e.* duration, intensity, assistance, type of control, interactivity, and use in parallel with other rehabilitation techniques (*e.g.* transcranial direct current stimulation, transcranial magnetic stimulation, virtual reality) and treatments (*e.g.* botulinum toxin).

References

1. Webster A, Poyade M, Rooney S, Paul L. Upper limb rehabilitation interventions using virtual reality for people with multiple sclerosis: A systematic review. Mult Scler Relat Disord 2021;47:102610.

2. Reyes F, Niedzwecki C, Gaebler-Spira D. Technological Advance-

ments in Cerebral Palsy Rehabilitation. Phys Med Rehabil Clin N Am 2020;31:117–29.

3. Chen Z, Wang C, Fan W, Gu M, Yasin G, Xiao S, *et al.* Robot-Assisted Arm Training versus Therapist-Mediated Training after Stroke: A Systematic Review and Meta-Analysis. J Healthc Eng 2020;2020:8810867.

4. Cheung EY, Ng TK, Yu KK, Kwan RL, Cheing GL. Robot-Assisted Training for People With Spinal Cord Injury: A Meta-Analysis. Arch Phys Med Rehabil 2017;98:2320–2331.e12.

5. Morone G, Cocchi I, Paolucci S, Iosa M. Robot-assisted therapy for arm recovery for stroke patients: state of the art and clinical implication. Expert Rev Med Devices 2020;17:223–33.

6. Duret C, Grosmaire AG, Krebs HI. Robot-Assisted Therapy in Upper Extremity Hemiparesis: Overview of an Evidence-Based Approach. Front Neurol 2019;10:412.

7. Masiero S, Poli P, Rosati G, Zanotto D, Iosa M, Paolucci S, *et al.* The value of robotic systems in stroke rehabilitation. Expert Rev Med Devices 2014;11:187–98.

8. Pollock A, Baer G, Langhorne P, Pomeroy V. Physiotherapy treatment approaches for the recovery of postural control and lower limb function following stroke: a systematic review. Clin Rehabil 2007;21:395–410.

9. van Peppen RP, Kwakkel G, der Wel BC, Kollen BJ, Hobbelen JS, Buurke JH, *et al.* 41. Hendriks HJM, Dekker J: guideline for stroke by KNGF. Nederlands Tijdschrift voor Fysiotherapie 2004;114:1–78.

10. Langhorne P, Coupar F, Pollock A. Motor recovery after stroke: a systematic review. Lancet Neurol 2009;8:741–54.

11. Cramer SC, Sur M, Dobkin BH, O'Brien C, Sanger TD, Trojanowski JQ, *et al.* Harnessing neuroplasticity for clinical applications. Brain 2011;134:1591–609.

12. Morone G, Spitoni GF, De Bartolo D, Ghanbari Ghooshchy S, Di Iulio F, Paolucci S, *et al.* Rehabilitative devices for a top-down approach. Expert Rev Med Devices 2019;16:187–95.

13. Turner DL, Ramos-Murguialday A, Birbaumer N, Hoffmann U, Luft A. Neurophysiology of robot-mediated training and therapy: a perspective for future use in clinical populations. Front Neurol 2013;4:184.

14. Basteris A, Nijenhuis SM, Stienen AH, Buurke JH, Prange GB, Amirabdollahian F. Training modalities in robot-mediated upper limb rehabilitation in stroke: a framework for classification based on a systematic review. J Neuroeng Rehabil 2014;11:111.

15. Mehrholz J, Pohl M, Platz T, Kugler J, Elsner B. Electromechanical and robot-assisted arm training for improving activities of daily living, arm function, and arm muscle strength after stroke. Cochrane Database Syst Rev 2018;9:CD006876.

16. Mehrholz J, Thomas S, Werner C, Kugler J, Pohl M, Elsner B. Electromechanical-assisted training for walking after stroke. Cochrane Database Syst Rev 2017;5:CD006185.

17. Morasso P, Casadio M, Giannoni P, Masia L, Sanguineti V, Squeri V, *et al.* Desirable features of a "humanoid" robot-therapist. Annu Int Conf IEEE Eng Med Biol Soc 2009;2009:2418–21.

18. Siciliano B, Sciavicco L, Villani L, Oriolo G. Robotics: Modelling, Planning and Control. Amsterdam: Springer; 2009

19. DocumentEU.32017R0745;2021[Internet].Availablefrom:https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32017R0745v [cited 2021, May 21].

20. FDA. Medical devices; 2021 [Internet]. Available from: https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/overview-device-regulation [cited 2021, May 21].

21. Tomassini V, Matthews PM, Thompson AJ, Fuglø D, Geurts JJ, Johansen-Berg H, *et al.* Neuroplasticity and functional recovery in multiple sclerosis. Nat Rev Neurol 2012;8:635–46.

22. Lamers I, Maris A, Severijns D, Dielkens W, Geurts S, Van Wijmeersch B, *et al.* Upper Limb Rehabilitation in People With Multiple Sclerosis: A Systematic Review. Neurorehabil Neural Repair 2016;30:773–93.

23. Li Z, Zhang X, Wang K, Wen J. Effects of Early Mobilization after Acute Stroke: A Meta-Analysis of Randomized Control Trials. J Stroke Cerebrovasc Dis 2018;27:1326–37.

24. AVERT Trial Collaboration group. Efficacy and safety of very early mobilisation within 24 h of stroke onset (AVERT): a randomised controlled trial. Lancet 2015;386:46–55.

25. Platz T, Kim IH, Pintschovius H, Winter T, Kieselbach A, Villringer K, *et al.* Multimodal EEG analysis in man suggests impairment-specific changes in movement-related electric brain activity after stroke. Brain 2000;123:2475–90.

26. Gandolfi M, Formaggio E, Geroin C, Storti SF, Boscolo Galazzo I, Bortolami M, *et al.* Quantification of Upper Limb Motor Recovery and EEG Power Changes after Robot-Assisted Bilateral Arm Training in Chronic Stroke Patients: A Prospective Pilot Study. Neural Plast 2018;2018:8105480.

27. Gandolfi M, Formaggio E, Geroin C, Storti SF, Boscolo Galazzo I, Waldner A, *et al.* Electroencephalographic Changes of Brain Oscillatory Activity After Upper Limb Somatic Sensation Training in a Patient With Somatosensory Deficit After Stroke. Clin EEG Neurosci 2015;46:347–52.

28. Formaggio E, Storti SF, Boscolo Galazzo I, Gandolfi M, Geroin C, Smania N, *et al.* Modulation of event-related desynchronization in robot-assisted hand performance: brain oscillatory changes in active, passive and imagined movements. J Neuroeng Rehabil 2013;10:24.

29. Qian Q, Nam C, Guo Z, Huang Y, Hu X, Ng SC, *et al.* Distal versus proximal - an investigation on different supportive strategies by robots for upper limb rehabilitation after stroke: a randomized controlled trial. J Neuroeng Rehabil 2019;16:64.

30. Iosa M, Morone G, Cherubini A, Paolucci S. The Three Laws of Neurorobotics: A Review on What Neurorehabilitation Robots Should Do for Patients and Clinicians. J Med Biol Eng 2016;36:1–11.

31. Hidler J, Nichols D, Pelliccio M, Brady K. Advances in the understanding and treatment of stroke impairment using robotic devices. Top Stroke Rehabil 2005;12:22–35.

32. Latash ML. On Primitives in Motor Control. Mot Contr 2020;24:318–46.

33. Pearcey GE, Zehr EP. We Are Upright-Walking Cats: Human Limbs as Sensory Antennae During Locomotion. Physiology (Bethesda) 2019;34:354–64.

Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Funding.—The present study was funded by a grant from the Italian Consensus Conference on "Rehabilitation assisted by robotic and electromechanical devices for persons with disability of neurological origin" (CICERONE), as promoted by the Italian Society of Physical and Rehabilitation Medicine (SIMFER, Società Italiana di Medicina Fisica e Riabilitativa), and Italian Society of Neurological Rehabilitation (Società Italiana di Riabilitazione Neurologica [SIRN]) (2019-2021).

Authors' contributions.— Marialuisa Gandolfi and Nicola Valè contributed equally. Marialuisa Gandolfi, Nicola Valè and Stefano Mazzoleni have given substantial contributions to the conception and design of the manuscript; Nicola Valè, Anita Botticelli, Eleonora Dimitrova, Antonella Dell'Orco, Jacopo Zenzeri, Elisa Gervasoni, Federico Posteraro and Michela Goffredo contributed to data acquisition, analysis and interpretation; all authors contributed to the manuscript draft and Marialuisa Gandolfi, Stefano Mazzoleni, Nicola Valè, Giovanni Morone, Elisa Gervasoni, Michela Goffredo, and Carla Daniele revised it critically. All authors read and approved the final version of the manuscript.

Group name.—Members of the group include the following: Eugenio GUGLIELMELLI (Campus Bio-Medico University, Rome, Italy); Nicola PETRONE (University of Padua, Padua, Italy); Loris PIGNOLO (Sant'Anna Institute, Crotone, Italy); Giulia SGUBIN (Italian Association of Physical Therapists

[AIFI], Rome, Italy); Nicola SMANIA (Unit of Neurorehabilitation, Department of Neuroscience, Biomedicine and Movement Sciences, University Hospital of Verona, University of Verona, Verona, Italy), Loredana ZOLLO (Campus Bio-Medico University, Rome, Italy).

Acknowledgements.—The authors acknowledge Giada Sturlese, Alessandro Salvini, Giulio Balestro, and Lucia Antolini for their editorial support activities.

History.—Article first published online: May 27, 2021. - Manuscript accepted: May 20, 2021. - Manuscript revised: May 14, 2021. - Manuscript received: March 5, 2021.

Supplementary data.—For supplementary materials, please see the HTML version of this article at www.minervamedica.it