

SYSTEMATIC REVIEW
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Rehabilitation and COVID-19: rapid living systematic review by Cochrane Rehabilitation Field – third edition.

Update as of June 30th, 2021

Maria G. CERAVOLO ¹, Elisa ANDRENELLI ¹, Chiara ARIENTI ², Pierre CÔTÉ ³, Alessandro de SIRE ⁴ *, Valerio IANNICELLI ⁵, Stefano G. LAZZARINI ², Francesco NEGRINI ⁵, Michele PATRINI ², Stefano NEGRINI ^{5,6}, The International Multiprofessional Steering Committee of Cochrane Rehabilitation REH-COVER Action ‡

¹Department of Experimental and Clinical Medicine, “Politecnica delle Marche” University, Ancona, Italy; ²IRCCS Fondazione Don Gnocchi, Milan, Italy; ³Faculty of Health Sciences, Ontario Tech University, Oshawa, ON, Canada; ⁴Department of Medical and Surgical Sciences, University of Magna Graecia, Catanzaro, Italy; ⁵IRCCS Istituto Ortopedico Galeazzi, Milan, Italy; ⁶Department of Biomedical, Surgical and Dental Sciences, University “La Statale”, Milan, Italy

‡Members are listed at the end of the paper.

*Corresponding author: Alessandro de Sire, Department of Medical and Surgical Sciences, University of Magna Graecia, Viale Europa, 88100 Catanzaro, Italy. E-mail: alessandro.desire@unicz.it

ABSTRACT

INTRODUCTION: This paper updates and summarizes the current evidence informing rehabilitation of patients with COVID-19 and/or describing the consequences of the disease and its treatment.

EVIDENCE ACQUISITION: Studies published from May 1st to June 30th, 2021 were selected, excluding descriptive studies and expert opinions. Papers were categorized according to study design, research question, COVID-19 phase, limitations of functioning of rehabilitation interest, and type of rehabilitation service involved. From this edition, we improved the quality assessment using the Joanna Briggs Institute checklists for observational studies and the Cochrane Risk of Bias Tool for randomized-controlled clinical trials (RCTs).

EVIDENCE SYNTHESIS: Twenty-five, out of 3699 papers, were included. They were three RCTs, 13 cross-sectional studies and nine cohort studies. Twenty studies reported data on symptom prevalence (N=13) or disease natural history (N=7); and five studies reported intervention effectiveness at the individual level. All study participants were COVID survivors and 48% of studies collected information on participants 6 months or longer after COVID-19 onset. The most frequent risks of bias for RCTs concerned weaknesses in allocation concealment, blinding of therapists, and lack of intention-to-treat analysis. Most analytical studies failed to identify or deal with confounders, describe or deal with dropouts or eventually perform an appropriate statistical analysis.

CONCLUSIONS: Most studies in this updated review targeted the prevalence of limitations of functioning of rehabilitation interest in COVID-19 survivors. This is similar to past review findings; however, data in the new studies was collected at longer follow-up periods (up to one year after symptom onset) and in larger samples of participants. More RCTs and analytical observational studies are available, but the methodological quality of recently published studies is low. There is a need for good quality intervention efficacy and effectiveness studies to complement the rapidly expanding evidence from observational studies.

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KEY WORDS: COVID-19; SARS virus; Coronavirus; Rehabilitation; Physical and rehabilitation medicine.

Introduction

Almost two years after the outbreak of the COVID-19 pandemic, the World Health Organization reports

about 4.6 million deaths and more than 220 million confirmed cases.¹ COVID-19 related mortality and morbidity risks are now mitigated by public health campaigns including vaccination. To date more than 5.3 billion vac-

cine doses have been administered.¹ A high proportion of SARS-CoV-2 patients survive infection but the prevalence of chronic sequelae and resulting disability is increasing. These survivors need clinical management and rehabilitation to facilitate good health outcomes. The best available research evidence is required to inform management and rehabilitation decisions, interventions, and health systems for COVID-19 survivors with adverse clinical sequelae. Further evidence is warranted to estimate the resources needed to plan for setting appropriate and adequately delivered post-acute and long-term rehabilitation services. To date, the ClinicalTrials.gov website² of the National Library of Medicine has registered more than 6400 clinical studies targeting the epidemiology and management of COVID-19, but only 245 studies (188 of which are ongoing) address rehabilitation in COVID-19 survivors.² This rapid living systematic review on rehabilitation and COVID-19 was initiated in April 2020 as a component of the Cochrane Rehabilitation REH-COVER action.³ Since its inception, it has been updated monthly, with the most recent update leading to a total of 319 papers up to April 30th, 2021. Most studies provided low-level descriptive evidence and we did not critically appraise their methodological quality. However, the recent increase in the number of analytical studies encouraged us to advance the methodology of the systematic review by adding critical appraisal of methodological quality to our narrative synthesis of evidence.

This paper aims to collate, critically appraise, and synthesize current best evidence relevant to the rehabilitation of patients with COVID-19, the consequences of the disease, and its treatment.

Evidence acquisition

The methodology of this systematic review updates the second edition published in June 2020.⁴ It follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Guidelines⁵ and the Interim Guidance from the Cochrane Rapid Reviews Methods Group.⁶ The protocol has been updated in PROSPERO (CRD42021181202).

The database search was conducted on July 2nd, 2021 covering publication dates between May 1st and June 30th, 2021. The search strategy, screening, and data extraction criteria were not changed from the previous edition⁴ except for the exclusion of case reports and case series. Additionally, to manage discrepancies encountered in past editions between the study design declared by the authors and the actual design of the study, we classified study designs according to the Agency for Healthcare Research and Qual-

ity⁷ (Supplementary Digital Material 1: Supplementary Text File 1).

We also expanded the evaluation of the quality of evidence using JBI checklists⁸ to appraise the methodological quality of observational studies and the Cochrane Risk of Bias Tool (RoB 1) to appraise methodological quality for randomized-controlled clinical trials (RCTs).⁹ Two review authors (C.A., V.I.) independently appraised the quality of studies and resolved disagreements by consensus; in the case of persistent disagreement, a third review author was consulted (P.C.) and the disagreement resolved by consensus.

To categorize participant samples, we adopted definitions agreed by the National Institute for Health and Care Excellence (NICE), Scottish Intercollegiate Guidelines Network (SIGN), and Royal College of General Practitioners (RCGP) that define acute COVID-19, ongoing symptomatic COVID-19, and post- COVID-19 syndrome, according to the duration of symptoms.^{10, 11}

This third edition still provides a narrative synthesis of findings, as a meta-analysis is not applicable due to the high heterogeneity of the studies. New studies were added to the consolidated online table of papers of all editions and to the interactive living evidence map available on the Cochrane Rehabilitation REH-COVER action website (https://tr.im/rr_dyn).

Evidence synthesis

We identified 7496 citations (3699 after removal of duplicates) from the databases. After title and abstract screening, we evaluated 120 studies and included 25 in the narrative synthesis (Figure 1). Table I, II, and III synthesize the distribution of selected studies by geographical area (Table I), limitations of functioning of rehabilitation interest (LFRI), disease phase and rehabilitation setting (Table II), research question, and study design (Table III).¹²⁻³⁶

Three papers presented RCTs,¹²⁻¹⁴ 13 were cross-sectional studies¹⁵⁻²⁷ and nine were cohort studies.²⁸⁻³⁶ Seventeen papers reported epidemiological data either on symptom prevalence (13 studies)¹⁵⁻²⁷ or disease natural history (seven studies),³⁰⁻³⁶ whereas five studies^{12-14, 28, 29} reported on intervention efficacy at the individual level. All study participants were COVID survivors and 48% of studies collected information on participants 6 months or longer after COVID-19 onset. Quality appraisal revealed the most frequent risks of bias for RCTs concerned weaknesses in allocation concealment, the lack of blinding of participants and providers, and the lack of intention-to-treat analysis

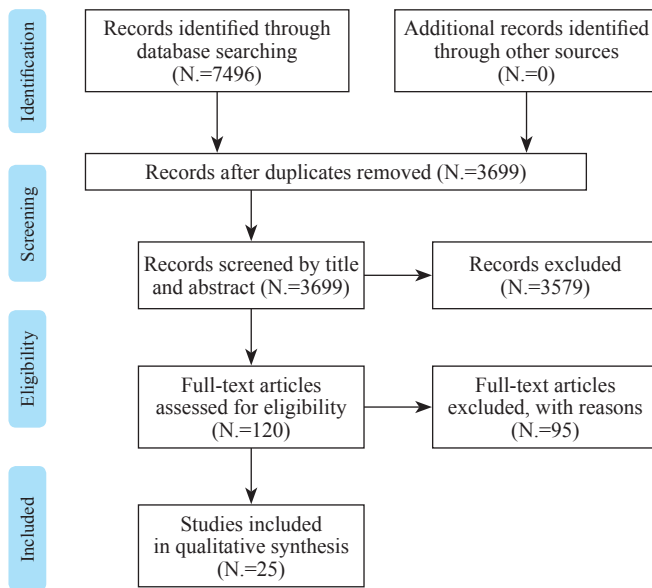


Figure 1.—PRISMA Flow Diagram.

TABLE I.—World Health Organization (WHO) regions and countries where studies were performed.¹²⁻³⁶

WHO Region	Country	N. (%)
European	Italy ^{25, 29, 31, 35}	4 (16%)
	Spain ²¹	1 (4%)
	Netherlands ^{20, 23}	2 (8%)
	Sweden ²⁶	1 (4%)
Americas	Turkey ¹⁵	1 (4%)
	Brazil ^{22, 27}	2 (8%)
Eastern Mediterranean	USA ^{16, 24, 28, 34, 36}	5 (20%)
	Pakistan ¹⁸	1 (4%)
Western Pacific	Iran ¹²	1 (4%)
	China ^{14, 19, 30, 32, 33}	5 (20%)
South-East Asia	India ¹³	1 (4%)
	Bangladesh ¹⁷	1 (4%)
Total		25 (100%)

TABLE II.—Distribution of studies by limitations of functioning of rehabilitation interest (LFRI), disease phase and rehabilitation setting.¹²⁻³⁶

Parameter	Classification	N. (%)
LFRI	Nervous system structures/functions ^{16, 25, 31, 35}	4 (16%)
	Respiratory structures/functions ^{13-15, 19, 20, 24, 27-29, 32}	10 (40%)
	Cardiovascular functions ^{33, 36}	2 (8%)
	Any other body structures and function ^{12, 17, 18, 21-23, 30}	7 (28%)
	Any activity limitation and participation restriction ^{26, 34}	2 (8%)
Disease phase	Acute covid-19 infection ^{12, 14}	2 (8%)
	Ongoing symptomatic COVID-19 ^{13, 16, 22, 24, 27-29, 31, 32, 35, 36}	11 (44%)
	Post-COVID-19 syndrome ^{15, 17-21, 23, 25, 26, 30, 33, 34}	12 (48%)
Rehabilitation setting*	Rehabilitation in acute care ¹⁴	1 (4%)
	Post-acute specialized ²⁹	1 (4%)
	Post-acute general ^{13, 21, 28, 35}	4 (16%)
	N/A ^{12, 15-20, 22-27, 30-34, 36}	19 (76%)

(Figure 2). The application of JBI checklists for observational studies revealed that most cross-sectional and cohort studies failed to identify or deal with confounders (Figure 3A, B), most cohort studies failed to describe or deal with dropouts (Figure 3B), and most prevalence studies did not perform an appropriate statistical analysis nor did they provide information useful to rate the adequacy of sample size, response rate, or data analysis (Figure 3C). Supplementary Digital Material 2 (Supplementary Table I) describes the output of the quality appraisal of each included study, grouped by design, whereas Supplementary Digital Material 3 (Supplementary Table II) details the main features and findings from the 25 selected studies. Below, we report a narrative synthesis of the study content with respect to the research questions.

Epidemiology: prevalence of LFRI

Most cross-sectional studies described the prevalence of LFRI in COVID-19 survivors. There is a growing amount of information collected for up to one year after COVID-19 onset, in large samples of patients.

Ongoing symptomatic COVID-19

Seven papers^{16, 22, 24, 27, 31, 32, 36} with cohort ranging from 23³¹ to 938²² participants (median value 71,5), described the clinical status and functioning of patients observed within 12 weeks from symptom onset. Among them, two studies^{24, 27} reported perceived persistent respiratory symptoms in at least 80% of participants, irrespective of the results of the pulmonary function tests. One study³⁶ described persistent symptoms in 80% of participants presenting with COVID-19-related cardiomyopathy. One study²² highlighted the protective role of vigorous physical activity towards the risk of hospitalization due to CO-

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TABLE III.—Distribution of studies by research question and study design.

Research question	RCTs	Cross-sectional studies	Cohort studies	Total
Epidemiology				
Clinical presentation	0	0	0	0
Prevalence	0	13 (52%)	0	13 (52%)
Natural history, determining and modifying factors	0	0	7 (28%)	7 (28%)
Micro-level: individuals	3 (12%)	0	2 (8%)	5 (20%)
Meso-level: health services	0	0	0	0
Macro-level: health systems	0	0	0	0
Total	3 (12%)	13 (52%)	9 (36%)	25 (100%)

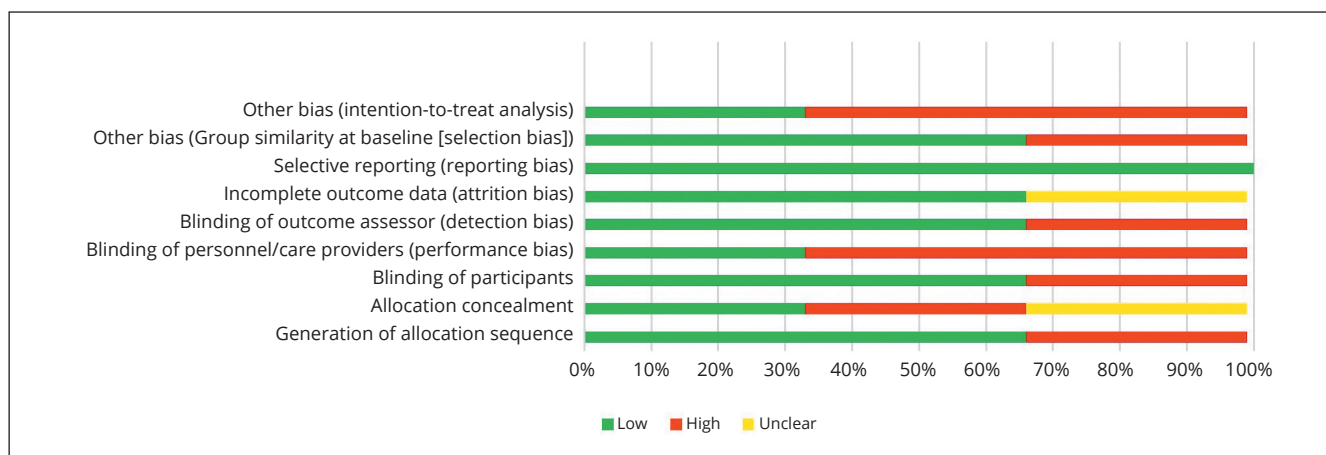


Figure 2.—Distribution of Risks of Bias in the included Randomized Controlled trials, according to the Cochrane Risk of Bias (RoB 1) tool.

VID-19. In this study, the following factors were associated with significant adverse outcomes: age >65 years, obesity, pre-existing disease, three or more symptoms, and using two or more medications.

Post-COVID-19 condition

Ten studies^{15, 17-21, 23, 25, 26, 30} with cohort sizes ranging from 30²¹ to 3677 participants³⁰ (median sample size: 238.5) reported on people presenting with the post-COVID-19 condition between 12 weeks and one year post symptom onset.¹⁹

Among them, four studies^{17, 18, 20, 30} described persistence of at least one of the following post-COVID-19 symptoms (fatigue; sleep disturbance; lack of concentration; breathing difficulty; headache or muscle pain) in 25% to 70% cases. Specifically, Sultana¹⁷ and Kashif¹⁸ reported that female sex and comorbid conditions were risk factors for long post-COVID symptoms.

Two studies^{23, 26} described activity limitations/participation restrictions and, more specifically, problems walking

>1 km, in 25% of patients more than four months after hospital discharge. Three studies confirmed the high prevalence of affective impairments (anxiety and depressive symptoms) as components of the post-COVID-19 syndrome^{21, 25, 26} Finally, one study¹⁹ found that about 40% of participants described persistent lung function impairment, likely due to pulmonary fibrosis, one year after recovering from COVID-19.

Epidemiology: natural history of LFRI

Two studies investigated the six-month level of functioning of people with COVID-19 who had survived neurological³⁴ or cardiac complications.³³ While Frontera³⁴ reported modified Rankin and Barthel index scores to be significantly worse in patients with neurological complications, no statistically significant differences were observed in terms of the quality of life and exercise capacity between the patients with and without cardiac injury.³³

One study suggests that severe COVID-19 survivors,

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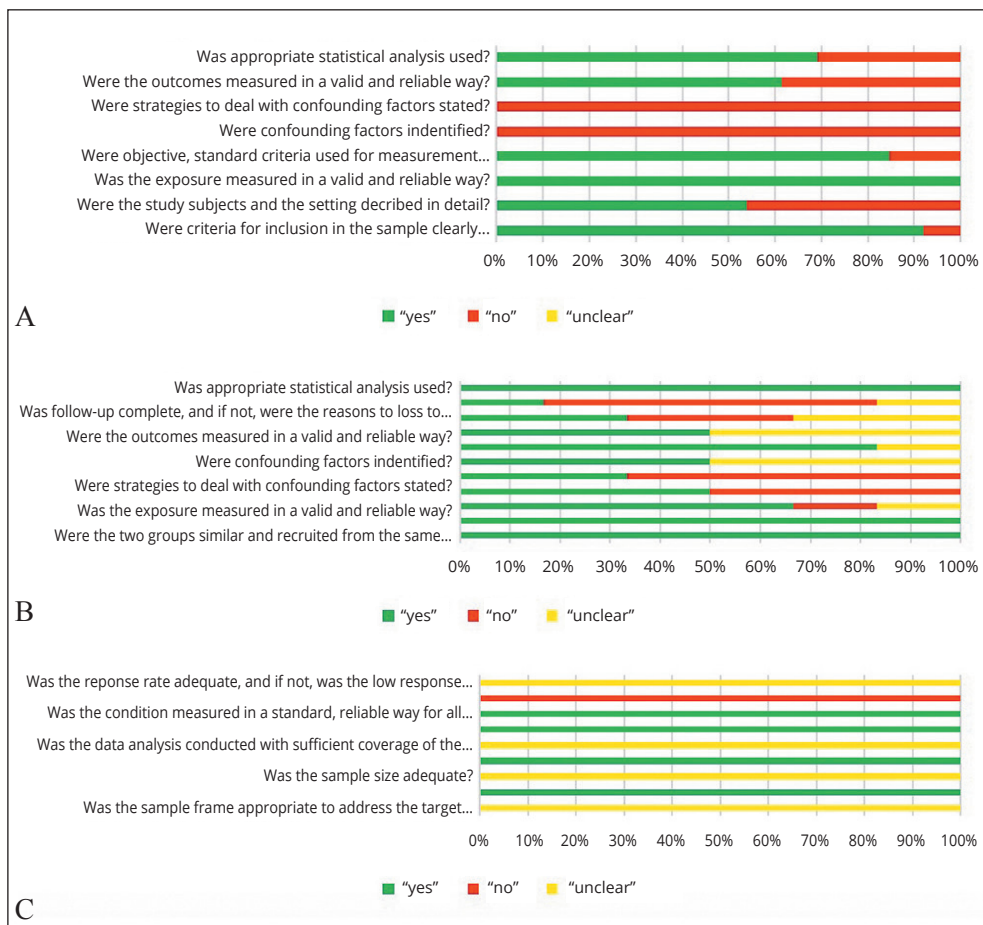


Figure 3.—Distribution of criteria for quality appraisal of observational studies according to JBI checklists for cross-sectional (A), cohort (B) and prevalence (inception cohort) (C) studies.

admitted to a COVID-19 rehabilitation unit, and assessed 10 days after symptom onset, showed lower scores in Mini Mental State Examination (MMSE) subtests of language and in several Montreal Cognitive Assessment (MoCA) subtests than people with mild and moderate disease, who, in contrast, reported significantly higher levels of distress, compared to the severe COVID-19 group.³⁵

Micro-intervention

Three RCTs¹²⁻¹⁴ reported on the effectiveness of rehabilitation interventions in COVID-19 patients. Two studies were conducted in the acute phase. One¹⁴ supported the greater effectiveness of short-wave diathermy (SWD) for recovering pulmonary symptoms when compared to placebo SWD; the other study¹² reported guided imagery therapy in addition to routine care was more effective than routine care alone on anxiety, muscle pain, and vital signs. The remaining RCT was conducted in the post-acute

phase¹³ and concluded that any combination of breathing exercises including pursed-lip breathing and the Bhastrika pranayama, performed at home, was effective at relieving ongoing respiratory symptoms.

Two cohort studies^{28, 29} described the outcome of COVID-19 patients admitted to inpatient rehabilitation facilities. The main findings were that COVID-19 participants with neurological or orthopedic complications showed the same functional recovery as people without COVID-19,²⁸ and that functional recovery in COVID-19 patients may not be affected by pre-existing comorbidities.²⁹

No study focused on intervention effectiveness at the service or system level.

Discussion

This third edition of the rapid living systematic review from the Cochrane Rehabilitation Field extends our knowledge about the consequences of COVID-19 and rehabilitation

management of sequelae across acute, ongoing symptomatic, and post-COVID-19 phases.

The review demonstrates an increased proportion of analytic observational studies focused primarily on the prevalence of respiratory and neurological impairments up to one year after COVID-19 onset. Most research is conducted in the European region, followed by the Americas and China; clinical populations include adults whose mean age varies from 35 to 66 years across studies. While three RCTs were identified, these, like all other included studies, revealed low methodological quality in critical appraisals. Overall, the impact of rehabilitation interventions on health outcomes could not be determined because meta-synthesis was not possible due to study heterogeneity.

The literature search was comprehensive with the search strategy replicating previous review editions that, to date, have been the most complete investigations of rehabilitation evidence related to COVID in health literature. In this third edition, one modification was introduced to the selection criteria to narrow the breadth of findings and increase the level of evidence sought by excluding case reports and case series. From a content point of view, it was clear that there was saturation of evidence on the clinical description of COVID-19 survivors in the literature – our clinical information need was about prevalence, natural history, and interventions. The applicability of findings was not affected by this change. Further, the use of a proven search strategy, screening, and interpretation of findings by a multidisciplinary rehabilitation team also support applicability to the clinical information need.

The methodological quality of the included studies was low with high risk of bias which limits generalizability and replication. This problem is not specific to rehabilitation and reported across many areas of COVID-19 biomedical research.³⁷ For example, Honarmand *et al.*³⁸ showed that 82.4% of trials had high or probably high risk of bias, 82.4% due to deviations from the intended intervention (including blinding) and 52.7% due to the randomization process (including allocation concealment and adequacy of the randomization procedure). The consequences are a production of low-quality evidence, which may be uninformative at best and may cause harm to patients. Therefore, it is becoming mandatory to consider the impact of trial quality to generate reliable, high quality evidence. The changes of our methodology highlight the needs to improve the quality of evidence, to be sure to guide the clinical decision-making on the management of COVID-19 disease.³⁹

From a clinical perspective, this systematic review con-

firms that COVID-19 is associated with disability in a high proportion of survivors one year after symptom onset. This disability is related to the persistence of respiratory dysfunctions, neurological and mental disorders. There is emerging evidence about the effectiveness of specific rehabilitation interventions at relieving respiratory symptoms and reducing the burden of disability

Conclusions

This rapid living systematic review of LFRI experienced by COVID-19 patients confirms the important impact of the disease on rehabilitation needs. The information gap about the course of functional recovery after the resolution of symptoms in people with and without complications is being filled by the increasing number of studies reporting on outcomes 6-12 month after COVID-19 onset. However, we still lack high-quality studies reporting on the efficacy and effectiveness of rehabilitation at the individual level, but more importantly at the service and system levels.

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Group name.—Members of the International Multiprofessional Steering Committee of Cochrane Rehabilitation REH-COVER (Rehabilitation for COVID-19: an Evidence-Based Response) Action include the following: Chiara ARIENTI (IRCCS Fondazione Don Gnocchi, Milan, Italy); Maria G. CERAVOLO (Department of Experimental and Clinical Medicine, Politecnica delle Marche University, Ancona, Italy); Pierre CÔTÉ (Faculty of Health Sciences, Ontario Tech University, Oshawa, ON, Canada); Anne CUSICK (Discipline of Occupational Therapy, The University of Sydney, Sydney, Australia); Wouter

DE GROOTE (Department of Noncommunicable Disease, World Health Organization, Geneva, Switzerland); Francesca GIMIGLIANO (Department of Mental and Physical Health and Preventive Medicine, Luigi Vanvitelli University of Campania, Naples, Italy); Allen W. HEINEMANN (Department of Physical Medicine and Rehabilitation, Northwestern University Feinberg School of Medicine, and Centre for Rehabilitation Outcomes Research, Shirley Ryan AbilityLab, Chicago, IL, USA); Carlotta KIEKENS (Spinal Unit, Montecatone Rehabilitation Institute, Imola, Bologna, Italy); Farooq RATHORE (Department of Rehabilitation Medicine, PNS Shifa Hospital, Karachi, Pakistan); Marco RIZZI (Unit of Infectious Diseases, ASST Papa Giovanni XXIII Hospital, Bergamo, Italy); Stefano NEGRINI (IRCCS Istituto Ortopedico Galeazzi, Milan, Italy); Department of Biomedical, Surgical and Dental Sciences, University “La Statale”, Milan, Italy); Geert VERHEYDEN (Department of Rehabilitation Sciences, KU Leuven – University of Leuven, Leuven, Belgium); Margaret WALSHE (Department of Clinical Speech and Language Studies, Trinity College Dublin, Dublin, Ireland).

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