



Minerva Access is the Institutional Repository of The University of Melbourne

Author/s:

Wingfield, M;Fini, NA;Brodtmann, A;Williams, G;Churilov, L;Hayward, KS

Title:

Upper-Limb Motor Intervention Elements That Drive Improvement in Biomarkers and Clinical Measures Post-Stroke: A Systematic Review in a Systems Paradigm

Date:

2022-11-01

Citation:

Wingfield, M., Fini, N. A., Brodtmann, A., Williams, G., Churilov, L. & Hayward, K. S. (2022). Upper-Limb Motor Intervention Elements That Drive Improvement in Biomarkers and Clinical Measures Post-Stroke: A Systematic Review in a Systems Paradigm. *Neurorehabilitation and Neural Repair*, 36 (10-11), pp.726-739. <https://doi.org/10.1177/15459683221129273>.

Persistent Link:

<https://hdl.handle.net/11343/333588>

Title: Upper-limb motor intervention elements that drive improvement in biomarkers and clinical measures post-stroke: A systematic review in a systems paradigm.

Authors:

Matthew Wingfield, BPhy, Department of Physiotherapy, University of Melbourne; Epworth Healthcare, Australia. mjwingfield@student.unimelb.edu.au

Natalie A Fini, PhD, Department of Physiotherapy, University of Melbourne, Australia. Natalie.fini@unimelb.edu.au

Amy Brodtmann, PhD, Cognitive Health Initiative, Central Clinical School, Monash University; Florey Institute of Neuroscience and Mental Health, University of Melbourne, Australia. agbrod@unimelb.edu.au

Gavin Williams, PhD, Departments of Physiotherapy, University of Melbourne, Epworth Healthcare, Australia. Gavin.willimas@epworth.org.au

Leonid Churilov, PhD, Melbourne Medical School, University of Melbourne, Australia. leonidc@unimelb.edu.au

Kathryn S Hayward, PhD, Departments of Physiotherapy, Medicine & Florey Institute of Neuroscience and Mental Health, University of Melbourne, Australia. kate.hayward@unimelb.edu.au

Corresponding Author:

Kathryn Hayward

Harold Stokes Building, Austin Hospital
Heidelberg, Australia

Email kate.hayward@unimelb.edu.au

Telephone: +61 03 9035 7293

Twitter: @kate_hayward_

Keywords: Stroke rehabilitation, upper extremity, biomarker, neuroplasticity, motor recovery

Subject terms: Rehabilitation, upper limb, stroke

Word count: 4327

Tables: 4

Figures: 2

Abstract

Objective: To use a systems paradigm to examine upper limb motor intervention elements driving biomarker and clinical measure improvement after stroke.

Methods: Databases were searched up to March 2022. Eligibility screening was completed by two authors. Studies using biomarkers and clinical measures pre- and post-upper limb intervention were included. Studies of adjunct interventions (e.g., brain stimulation) were excluded. Cochrane Risk-of-Bias tools and Template for Intervention Description and Replication were used to rate studies. Studies were synthesised using a systems paradigm: intervention outcome was considered an emergent property of the systemic interactions of four intervention elements (demographics, type, quality, and dose) characterised by individual dimensions.

Results: Sixty-four studies (n=1814 participants) containing 106 intervention groups (66 experimental; 40 control) were included. Combined biomarker and clinical outcomes defined three scenarios: restitution, mixed, and unchanged. The restitution scenario included more moderate-to-severely impaired participants in earlier recovery phases (<6months). Interventions with graded difficulty were more frequently used in the restitution scenario compared to those with the unchanged scenario. No difference in quality or amount of therapy was identified when examining scenarios that demonstrated restitution compared to those that did not (mixed and unchanged).

Conclusions: A systems paradigm may be one of many approaches to understand upper limb motor restitution. This review found no single element consistently delivered improvements in biomarkers and clinical measures in the examined intervention groups. Complex patterns formed by multiple interacting intervention elements were observed in participants with and without restitution.

Key words: Upper Extremity, Stroke rehabilitation, motor recovery, neuroimaging, outcomes

Non-standard Abbreviations and Acronyms

Risk of Bias (RoB)

Template for Intervention Description and Replication (TIDieR)

Constraint Induced Movement Therapy (CIMT)

Minimal clinically important difference (MCID)

Upper limb (UL)

Randomized controlled trial (RCT)

Introduction

Upper limb (UL) motor recovery remains a priority for stroke survivors¹ and has been identified as a key research area^{1,2}. Up to 80% of stroke survivors present with UL disability early after stroke³. While recent advances in acute stroke interventions, such as endovascular clot retrieval have dramatically changed the expectations for recovery, not all stroke survivors are eligible for these treatments⁴. For stroke survivors with persistent UL disability⁵, engagement in motor interventions is their pathway to recovery. This has yet to be fully optimized.

Current aspirational views of recovery focus on the ability of motor interventions to deliver restitution⁶. The international Stroke Recovery and Rehabilitation Roundtable defined restitution as a “return towards more normal patterns of motor control”⁶. As restitution reflects true recovery, it requires neurological recovery in parallel with motor recovery⁶. Empirical measurement of restitution after stroke has been challenging. The stroke recovery field has relied on biomarkers and clinical measures to provide a window to infer what may have occurred during the neurological and motor recovery processes. The Roundtable defined a biomarker as a “measure of the underlying molecular/cellular processes”⁷. When indexed longitudinally, improvement in brain biomarkers that measure structure or function may reflect neurological recovery⁷. Motor recovery may be examined using measures of impairment and activity⁸ and both are important to uniquely examine change over time. Measures of UL impairment infer recovery of the individual’s body structure and function, while UL activity measures infer recovery of the individual's ability to execute a task or action⁹. Therefore, to interrogate restitution (neurological + motor recovery), it is imperative for a given intervention to demonstrate parallel improvements in biomarkers, impairment measures, and activity measures^{6,10,11}. This novel strategy to interrogate restitution may yield a unique perspective that can guide the identification of successful UL motor interventions.

Upper limb motor interventions should be considered complex by any definition¹²⁻¹⁴. Prior research¹⁵⁻¹⁷ indicates that numerous elements, such as dose¹⁸, type¹⁹, and quality¹², have been routinely applied in UL motor interventions to drive recovery. In clinical trials, these elements (e.g., type and dose) and their multiple dimensions (e.g., dose: duration and difficulty; type: treatment and delivery method) have largely been explored in a factorial paradigm, where effects of individual elements are studied either individually or as two-way interactions between elements. While this approach has often been unsuccessful in shifting recovery profiles^{5,20}, it reflects underlying feasibility constraints and the confirmatory nature of clinical trials. Importantly though, it has guided the evolution of our understanding of motor interventions from simple to complex.

A systems paradigm^{21,22} presents an alternative perspective on the inherent complexity of motor interventions^{23,24}. In such a paradigm, intervention outcomes would be conceptualized as *emergent properties* of the interaction between individual system elements and dimensions. It would postulate that restitution is the result of all the multidimensional elements of the intervention working in an integrated manner. No individual intervention element or dimension could be modified without affecting the resulting restitution outcome. Therefore, a systems paradigm places emphasis on the consideration of numerous elements and dimensions integral to the design and operation of said intervention, and acknowledgement of the elements' interrelatedness.

Use of a systems paradigm, and subsequent shift in analytic emphasis, could help explain why similar interventions produce different outcomes in different contexts. This could bring more clarity as to *how* and *why* outcomes were achieved. Understanding *how* and *why* intervention elements drive restitution may guide the field to better exploit these elements and capitalize on restitution of UL function post-stroke. This may have downstream effects on lost wellbeing and premature mortality, experienced by stroke survivors²⁵.

Therefore, we aimed to identify and examine multidimensional elements of UL motor interventions in a systems paradigm and investigate their relationship to biomarkers and clinical measures of recovery after stroke via systematic review.

Methods

The definitions of key terms guiding the conduct of this systematic review are outlined in Table 1.

Table 1. Definitions of terms used in this systematic review	
Terminology	Definition
Restitution	Return towards more normal patterns of motor control with the impaired UL and reflects the process towards true recovery ⁶ . Requires neurological recovery and motor recovery to occur in parallel. ²⁶
Biomarker	Measures of brain function or structure that can be indexed longitudinally; a measure of the underlying molecular/cellular process ⁷ .
Clinical Measures	Outcomes used in clinical practice that index a change in motor performance. Can be across multiple domains of the WHO-ICF ⁸ : impairment (impairment measures), or activity (activity measures) ¹¹ .
Neurological recovery	The process of improvement towards more normal neurological function or structure. Inferred by improvement in biomarkers.

Motor recovery	The process of improvement towards more normal motor function. Inferred by improvements in impairment and activity measures in parallel.
----------------	--

This systematic review was prospectively registered on the Prospective Register of Systematic Reviews (CRD42020206967). The Preferred Reporting Items for Systematic Reviews and Meta-Analysis 2020 statement provided the framework for reporting²⁶.

Information Sources and Search Strategy

Searches were conducted in MEDLINE, EMBASE and Cochrane Controlled Register of Trials databases on March 13, 2022. Medical Subject Heading terms and a combination of relevant keywords were used (see supplemental I).

Eligibility Criteria

The search yield was imported into Covidence²⁷ and duplicates removed. Eligibility was examined by two reviewers (MW, and one of NF or KH). All titles/abstracts and full texts were independently appraised. All studies were screened against predetermined eligibility criteria. Hand searching of included study reference lists and relevant reviews were completed to identify additional studies. We attempted to link identified abstracts from conference proceedings with full-text peer-reviewed papers where possible. Disagreements regarding eligibility were resolved through discussion (MW/NF/KH).

Design: Peer-reviewed randomized, non-randomized or single group studies published in English that aimed to explore recovery of UL impairment or activity post-stroke in any setting (i.e., inpatient, outpatient, home) and via any mode of delivery (i.e., in-person, individual/group, telehealth) were eligible. Each study required a minimum of 10 participants, which is consistent with a prior Cochrane review²⁸. Grey literature and all other designs were excluded, including single case and systematic reviews.

Participants: Studies that enrolled adult (≥ 18 years) human stroke survivors, of any stroke type or time post-stroke onset⁶ were eligible. Preclinical studies (e.g., animal studies) and non-stroke participants, including mixed diagnosis cohorts, were excluded.

Interventions: Interventions designed to improve UL motor function (impairment or activity) were eligible. Any study without an active intervention group was excluded. Any pharmacological, complimentary (e.g., acupuncture), non-invasive brain stimulation (e.g., transcranial direct current stimulation), priming (e.g., repetitive transcranial magnetic stimulation), or brain driven robotic (e.g., brain computer interface) interventions in combination with or without a motor intervention were excluded.

Outcomes: Studies must have included a biomarker that indexed brain structure or function, in addition to a measure of UL motor impairment or activity both pre- and post-intervention. Studies that measured general motor function (e.g., activities of daily living) or participation⁸ (e.g., Stroke Impact Scale) were excluded, as well as studies with only a pre-intervention (baseline) biomarker.

Risk of Bias and Intervention Reporting

One author (MW) rated Risk of Bias (RoB) using Version 2 of the Cochrane Risk-of-Bias Tool²⁹ for randomized controlled trials (RCT) or the RoB In Non-Randomized Studies – of Interventions³⁰ for non-RCTs and single group intervention trials. Each study was subject to a separate RoB examination for both clinical measures and biomarkers (supplemental II & III). The highest RoB rating across all sections of either tool was reported as overall RoB (Table 4). Intervention reporting was examined using the Template for Intervention Description and Replication Checklist (TIDieR)¹⁵. Twenty percent of the RoB and TIDieR ratings were double rated (KH).

Synthesis Methods

Elements and Dimensions Taxonomy

Each control and experimental group, herein referred to as intervention group, were deconstructed into dimensions based on TIDieR checklist¹⁵ and dose articulation framework¹⁷. The TIDieR checklist was chosen due to the rigorous methods used in its development and alignment with intervention reporting¹⁵. The dose articulation framework was chosen due to its appreciation of the multidimensional nature of dose as an intervention element. Similar dimensions were collated under a consistent element. The system we sought to investigate contains four elements (demographics, type, quality, and dose) made from 16 different dimensions. If the study reported information relevant to the TIDieR item (and subsequent dimension) the information was recorded according to taxonomy developed for this review (Table 2 & Supplemental IV). If there was no information reported relevant to the TIDieR item (and subsequent dimension) it was recorded as “not reported”. Table 2 defines the elements and dimensions extracted for each intervention group, corresponding TIDieR items, and example application of this taxonomy.

Table 2. Taxonomy of elements and dimensions			
Elements	Dimensions	TIDieR	Example: El Helow ³² (2015) control group
Demographic	Recovery Phase	N/A	Early Subacute
	Severity	N/A	Moderate
Type	Treatment	1&3	CIMT
	Setting	7	Inpatient
	Method of Delivery	6	Face-to-face
	Group/Individual	6	Individual

Quality	Therapist Training	5	Yes
	Tailoring	9	Yes
	Fidelity	11&12	Yes
Dose	Duration	8	2weeks
	Days	8	10days
	Sessions/day	8	1/day
	Length of sessions	8	8hours
	Total hours of therapy	8	80hours
	Difficulty progression	8	Not reported
	Intensity	8	Not reported

Classification of Recovery Phase

Studies were classified according to the Stroke Recovery and Rehabilitation Roundtable definitions⁶: acute, 1-7days; early subacute, 7days-3months; late subacute, 3months-6months; chronic, >6months. Classification was made according to the intervention group's mean time since stroke onset. If insufficient information was given the group was classified as 'unable to classify'.

Classification of Severity

Studies were classified by participant severity using the mean of a clinical measure (UL e.g., Fugl Meyer Upper Limb (FMUL), or general stroke scale e.g., National Institutes of Health Stroke Scale (NIHSS)) using established categories (supplemental V). If studies did not use a clinical measure to define severity, study terminology i.e., mild, moderate, or severe was used. If there was no clinical measure that could be used to classify severity and no indication was given within the study, studies that stated an inclusion criterion of >10 degrees of voluntary finger extension were classified as mild, consistent with previous literature³¹.

One other study was classified as moderate using baseline Action Research Arm Test (ARAT) summary scores using available literature³².

Classification of Treatment Type

Treatment type were categorized as bilateral arm training, biofeedback, Bobath approach, constraint induced movement therapy (CIMT), electrical stimulation, “hands on” manual therapy techniques, mental practice or mirror therapy, music therapy or repetitive task training or task specific training, electromechanical interventions including robotics, strength training, virtual reality training or standard therapy¹⁹. For data synthesis, similar treatment types were combined, such as repetitive task practise and task specific practise as both targeted high-volume task repetition.

Classification of Outcome Measures

Biomarkers were classified as measuring brain function or structure⁷. Changes in biomarkers, that were reported as statistically significant by each individual study and were in keeping with the changes outlined in Table 3, constituted improvement. Severity was an important consideration when defining improvements in biomarkers as mildly impaired stroke survivors may demonstrate different changes in biomarkers compared with moderate-severe survivors³³⁻³⁵. Table 3 provides a summary of each biomarker, priority ranking, and justification for rating improvement.

Table 3: Summary of biomarkers						
Modality	Function/Structure	Metric (In order of priority)	Population severity	Justification		
				Improvement	No change	Regression
Transcranial magnetic stimulation (TMS)	Function	1. Motor Evoked Potential (MEP) amplitude ¹	Mild, Mod, and Severe	Increase measured in millivolts (mV), reported as significant by the study.	No significant change	Decrease measured in mV, reported as significant by the study.
		2. Resting Motor Threshold (rMT) ¹		Decrease measured in mV, reported as significant by the study.	No significant change	Increase measured in mV, reported as significant by the study.
		3. Central motor conduction time (CMCT) ¹		Reduction measured in milliseconds (ms), reported as significant by the study.	No significant change	Increase measured in ms, reported as significant by the study.
		4. MEP presence ²		Increase in number patients with a MEP, reported as significant by the study.	No significant change	Decrease in number patients with a MEP, reported as significant by the study.

Functional magnetic resonance imaging (fMRI)	Function	BOLD signal activation voxel count	Mild	Increased signal ipsilesional primary motor cortex activation in the absence of contralesional activation ³ . 'Focusing' reported as significant by the study.	No significant change	Increased signal in motor structures ipsilesional ³ . 'Recruitment' reported as significant by the study.
			Moderate and Severe	Increased signal in motor structures contralesionally or ipsilesional ³ . 'Recruitment' reported as significant by the study.	No significant change	N/A
Functional near infra-red stimulation (fNIRS)	Function	BOLD signal activation voxel count	Mild	Increased signal ipsilesional primary motor cortex activation in the absence of contralesional	No significant change	Increased signal in motor structures ipsilesional ³ . 'Recruitment' reported as significant by the study.

				activation ³ . ‘Focusing’ reported as significant by the study.		
			Moderate and Severe	Increased signal in motor structures contralesionally or ipsilesional ³ . ‘Recruitment’ reported as significant by the study.	No significant change	N/A
Electro-encephalography (EEG)	Function	Task Related Coherence (TRCoh)	Mild, Mod, and Severe	Improved TRCoh occurs ⁴ reported as significant by the study.	No significant change	Reduction in TRCoh, reported as significant by the study.
Resting state fMRI (rsfMRI) and Single-photon emission computed tomography	Function	Functional Connectivity (strength of connections)	Mild, Mod, and Severe	Improved synchronicity in, motor regions at resting state ⁵ , reported as significant by the study.	No significant change	Reduction in synchronicity in motor regions at resting state, reported as significant by the study.

T1 Magnetic resonance imaging (T1 MRI)	Structure	Grey Matter Volume	Mild, Mod, and Severe	Increases in grey matter volume in primary motor cortex ⁶ , reported as significant by the study.	No significant change	Reduction in grey matter volume in primary motor cortex, reported as significant by the study.
Diffusion Tensor imaging (DTI)	Structure	Fractional Anisotropy	Mild, Mod, and Severe	Increase in fractional anisotropy ⁷ , reported as significant by the study	No significant change	Reduction in fractional anisotropy, reported as significant by the study

Clinical measures were classified as either impairment or activity³⁶ (supplement VI). To demonstrate improvement in clinical measures, each intervention group must have achieved the defined minimal clinically important difference (MCID) for the specific measure demonstrated by change from pre- to post-intervention. If no MCID was available in the literature, a 20% improvement was required. This 20% cut-off falls within evidence-based MCIDs reported for other UL measures post-stroke³⁷. The applied MCIDs are outlined in supplemental VI.

Data Extraction

Data from each study were extracted by one author (MW) and 20% were cross checked by a second author (KH). Two authors (MW/KH) discussed any unclear data to reach consensus. Intervention data were extracted in keeping with past reviews¹⁷ and included participant demographics, intervention elements, biomarkers, impairment, and activity measures (Supplemental IV). If raw data were not provided, PlotDigitizerV2.6.9 interpretive software was used to extract the data from figures. If more data was required, the corresponding author was contacted (maximum three emails).

Data Analysis

Demographic and other data were collated in a custom-built Excel spreadsheet and summarized e.g., overall number of participants, outcome measures used. Biomarkers and UL clinical measures were classified as improved, no change, or regressed (see Table 3 & supplemental VI). Each dimension (Table 2) was analysed dichotomously (reported or not). Dose dimensions were simplified to hours per day of therapy for consistency across studies. Dose was then dichotomised to whether the intervention group received a potentially important threshold for motor recovery (2 hours per day)³⁸. Integrating outcomes on

biomarkers and clinical measures classified each intervention group (i.e., experimental and control) into three possible outcome scenarios:

- a) Restitution, groups that demonstrated parallel improvements in biomarkers, impairment, and activity measures.
- b) Mixed, groups that demonstrated improvements in either a biomarker, impairment, or activity measure in any combination.
- c) Unchanged, groups that demonstrated no change across biomarkers, impairment, and activity measures.

The restitution scenario elements were compared to a combined (mixed and unchanged) scenario. The mixed and unchanged scenarios were subsequently separated for a more nuanced comparison within each of these scenarios. Radar plots were created using Microsoft Excel version 2101 (Build 14827.20198). The results were descriptively reported.

Results

Search Results

The search strategy yielded 5317 studies after duplicates were removed (CENTRAL n=227, EMBASE n=3784, Medline n=1306). A total of 201 full texts were reviewed. The PRISMA flow chart for the identification and inclusion of studies is provided in supplemental VII. The final yield was 64 studies (RCT n=34; non-RCT n=6; single group n=24). The reasons for exclusion at full text were related to the intervention (n=51), study design (n=46), sample size <10 (n=24), duplication (n=12) and absence of outcome measure (n=4). A list of excluded references from full-text screening is provided in supplemental VIII. From the 64 included studies, there were 106 intervention groups (66 experimental and 40 control). Summary of all included studies is provided in supplemental IX and corresponding references are provided in supplemental X.

Population Demographics

A total of 1,814 participants were included (women $n=581$, men $n=1069$, not reported $n=164$). Most intervention groups included participants with moderate motor impairment ($n=45$, 42%) followed by mild ($n=38$, 36%) and severe ($n=23$, 22%). Participant groups were commonly in the chronic phase of recovery ($n=59$, 56%) followed by early sub-acute ($n=31$, 29%) and late subacute ($n=8$, 8%). Of the 106 intervention groups: 12 used structural biomarkers, 99 used functional biomarkers, 70 used impairment measures, and 80 used activity measures.

Risk of Bias

Most studies were rated moderate RoB ($n=32$, 50%), followed by high or critical ($n=26$, 41%) and low ($n=6$, 9%) (Table 4 and supplement II).

Intervention Reporting

The median TIDieR score was 6. All studies reported intervention “name” i.e., treatment type. The poorest items reported were: “who provided?”, i.e., therapist training (11%), and “how well (planned)?” (10%). See Figure 1A. The most frequently reported element was demographics (98%). The least frequently reported element was quality (33%) of data points were reported. Reporting of elements and dimensions can be seen in Figure 1B.

Figure 1.

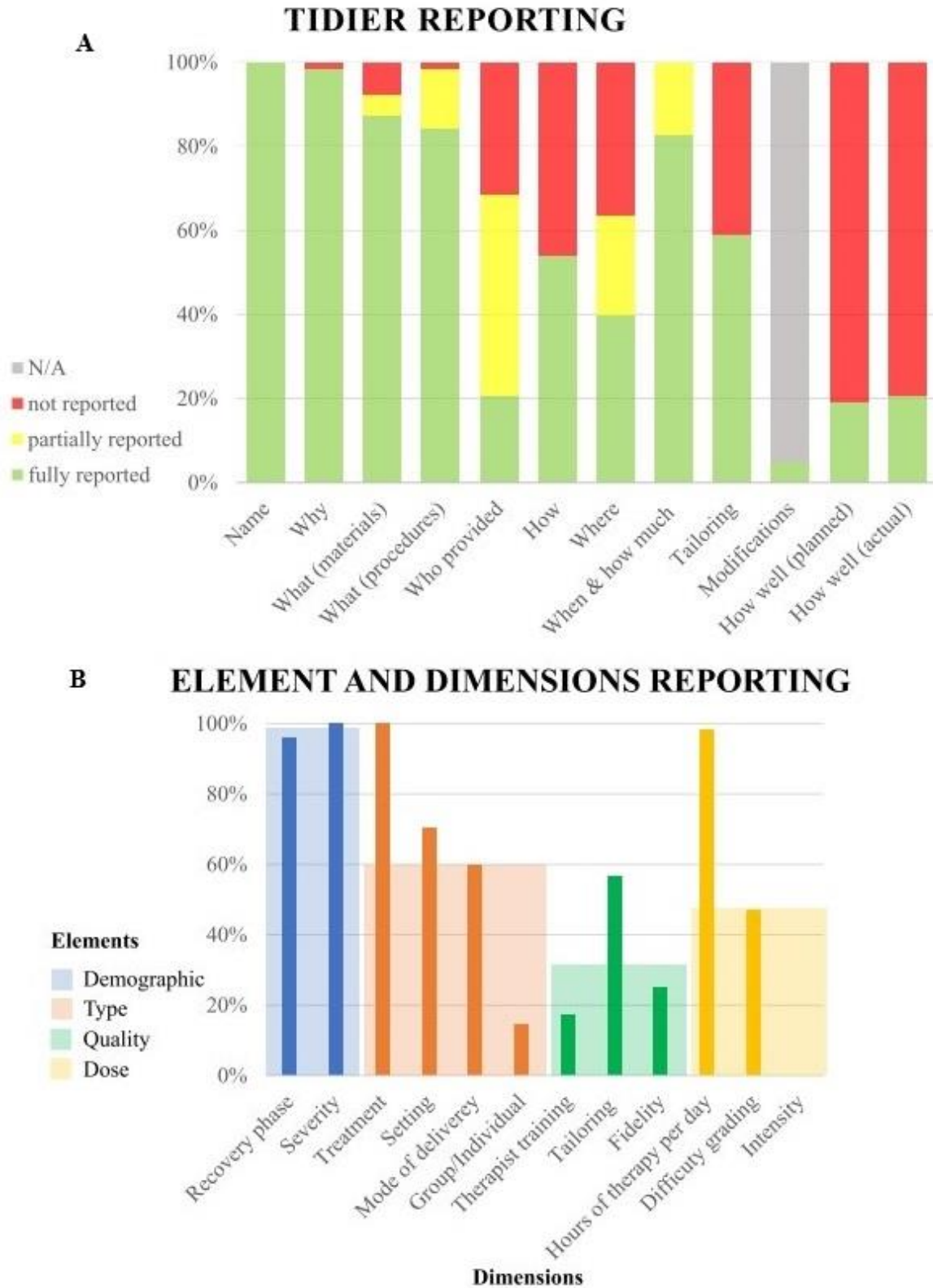


Figure 1: A. TIDieR reporting. N/A = not applicable. B. Reporting of elements and dimensions

Outcome Measures

Biomarkers

Structural biomarkers were included in 12 intervention groups using either diffusion-weighted diffusion tensor imaging ($n=6$) or T1-weighted/MPRAGE structural magnetic resonance imaging ($n=6$). Functional biomarkers were included in 99 intervention groups, with transcranial magnetic stimulation ($n=44$) and functional magnetic resonance imaging ($n=40$) used the most. Five intervention groups (5%) used both structural and functional biomarkers simultaneously.

An improvement in a structural biomarker was reported in only four intervention groups; remaining groups indicated no change. No groups regressed on a structural biomarker. Improvement on a functional biomarker was observed in 49 intervention groups and no changes were evident in 49 intervention groups. One intervention group³⁹ demonstrated a regression on a functional biomarker as defined by this review. This study demonstrated recruitment of supra-normal contralesional motor areas in a population with mild UL impairment. Of the five intervention groups that used both a structural and functional biomarker, one intervention group improved on its structural biomarker but demonstrated no change on the functional biomarker used⁴⁰. The remaining four intervention groups demonstrated no change across both the structural and the functional biomarker used.

Clinical Measures

Only 44 intervention groups included both an impairment and activity measure. Impairment measures were included in 70 intervention groups, and Fugl Meyer UL ($n=58$) was the most common. Activity measures were included in 80 intervention groups, and Wolf Motor Function Test ($n=35$) was the most common. A MCID was achieved in 39 intervention groups that measured impairment and 41 intervention groups that measured activity. No intervention group regressed on either impairment or activity measures. Sixteen intervention

groups achieved a MCID on both impairment and activity measures, while 19 intervention groups did not demonstrate an MCID across both measures. Five intervention groups demonstrated a MCID on an impairment measure while not achieving a MCID on the activity measure used in parallel. Four intervention groups demonstrated a MCID on an activity measure while not achieving a MCID in the impairment measure used in parallel.

Biomarkers and Clinical Measures

Only four intervention groups included all four measures: i.e., a structural and functional biomarker, and an impairment and activity measure. None of these intervention groups demonstrated improvement across all four measures. There were 44 intervention groups that included a functional biomarker and both an impairment and activity measures. Seven of these intervention groups improved across all three measures. Eleven intervention groups demonstrated no change in biomarker and did not achieve an MCID in either impairment or activity measures. Eight intervention groups improved on both impairment and activity measures despite no change on a functional biomarker. There were no groups that included a structural biomarker and both impairment and activity measures. A summary of results on biomarkers and clinical measures are provided in Table 4.

Table 4: Results Summary							
Study Design	Author (Year)	Control Group Vs Experimental Group	Biomarker		Clinical Measure		Risk of Bias
			Structural	Functional	Impairment	Activity	
RCT	Ballester (2017)	Control	N/A	-	-	-	Some Concerns
RCT	Ballester (2017)	Experimental	N/A	↑	-	-	
RCT	Bhatt (2007)	Control	N/A	-	-	-	Some Concerns
RCT	Bhatt (2007)	Experimental ^a	N/A	-	-	-	
RCT	Bhatt (2007)	Experimental ^b	N/A	-	-	-	
RCT	Boake (2007)	Control	N/A	-	↑	↑	Some Concerns
RCT	Boake (2007)	Experimental	N/A	-	↑	↑	
RCT	Calabrò (2019)	Control	N/A	↑	-	-	Some Concerns
RCT	Calabrò (2019)	Experimental	N/A	↑	↑	-	
RCT	Carey (2007)	Control	N/A	↑	-	↑	High
RCT	Carey (2007)	Experimental	N/A	-	↑	↑	
RCT	De Bruyn (2021)	Control	N/A	-	↑	↑	High

RCT	De Bruyn (2021)	Experimental	N/A	-	↑	-	
RCT	Dechaumont-Palacin (2008)	Control	N/A	↑	-	N/A	High
RCT	Dechaumont-Palacin (2008)	Experimental	N/A	-	-	N/A	
RCT	Dehno (2021)	Control	N/A	↑	↑	N/A	Some Concerns
RCT	Dehno (2021)	Experimental	N/A	↑	↑	N/A	
RCT	Ding (2019)	Control	N/A	-	↑	N/A	Some Concerns
RCT	Ding (2019)	Experimental	N/A	-	↑	N/A	
RCT	El-Helow (2015)	Control	N/A	-	-	-	Low
RCT	El-Helow (2015)	Experimental	N/A	↑	↑	↑	
RCT	Fu (2017)	Control	N/A	↑	↑	↑	High
RCT	Fu (2017)	Experimental	N/A	↑	↑	↑	
RCT	Gauthier (2008)	Control	-	N/A	N/A	↑	Some Concerns
RCT	Gauthier (2008)	Experimental	↑	N/A	N/A	↑	
RCT	Hammerback (2021)	Control	N/A	-	↑	N/A	Low
RCT	Hammerback (2021)	Experimental	N/A	-	↑	N/A	
RCT	Hubbard (2015)	Control	N/A	-	N/A	↑	Low

RCT	Hubbard (2015)	Experimental	N/A	-	N/A	↑	
RCT	Hunter (2018)	Control	-	-	-	↑	Some Concerns
RCT	Hunter (2018)	Experimental	-	-	↑	↑	
RCT	Kimberley (2004)	Control	N/A	-	-	-	Some Concerns
RCT	Kimberley (2004)	Experimental	N/A	-	-	-	
RCT	Li (2018)	Control	-	-	-	-	Some Concerns
RCT	Li (2018)	Experimental	↑	-	-	↑	
RCT	Lin (2010)	Control	N/A	-	-	-	Some Concerns
RCT	Lin (2010)	Experimental	N/A	↓	↑	↑	
RCT	Lui (2014a)	Control	N/A	-	N/A	-	High
RCT	Lui (2014a)	Experimental	N/A	↑	N/A	↑	
RCT	Luft (2004)	Control	N/A	-	-	↑	Some Concerns
RCT	Luft (2004)	Experimental	N/A	↑	-	-	
RCT	Mekbib (2021)	Control	N/A	↑	-	N/A	Some Concerns
RCT	Mekbib (2021)	Experimental	N/A	↑	-	N/A	
RCT	Michielsen (2011)	Control	N/A	-	-	-	High

RCT	Michielsen (2011)	Experimental	N/A	↑	-	-	
RCT	Pelicioni (2016)	Control	N/A	↑	↑	-	Some Concerns
RCT	Pelicioni (2016)	Experimental	N/A	↑	↑	↑	
RCT	Platz (2005)	Control	N/A	-	↑	N/A	Some Concerns
RCT	Platz (2005)	Experimental ^c	N/A	-	↑	N/A	
RCT	Platz (2005)	Experimental ^d	N/A	-	↑	N/A	
RCT	Singh (2021)	Control	N/A	-	↑	N/A	High
RCT	Singh (2021)	Experimental	N/A	↑	↑	N/A	
RCT	Sterr (2013)	Control	↑	N/A	N/A	↑	High
RCT	Sterr (2013)	Experimental	↑	N/A	N/A	-	
RCT	Summers (2007)	Control	N/A	-	N/A	-	Some Concerns
RCT	Summers (2007)	Experimental	N/A	-	N/A	-	
RCT	Takahashi (2008)	Control	N/A	↑	↑	-	Some Concerns
RCT	Takahashi (2008)	Experimental	N/A	↑	↑	-	
RCT	Tarkka (2011)	Control	N/A	-	N/A	-	High
RCT	Tarkka (2011)	Experimental	N/A	-	N/A	↑	

RCT	Waller (2014)	Control	N/A	-	-	-	Some Concerns
RCT	Waller (2014)	Experimental	N/A	↑	↑	↑	
RCT	Wang (2017)	Control	N/A	↑	N/A	-	Some Concerns
RCT	Wang (2017)	Experimental	N/A	↑	N/A	↑	
RCT	Whitall (2011)	Control	N/A	↑	-	-	Some Concerns
RCT	Whitall (2011)	Experimental	N/A	↑	-	-	
RCT	Xie (2021)	Control	N/A	↑	↑	N/A	Some Concerns
RCT	Xie (2021)	Experimental	N/A	↑	↑	N/A	
RCT	Yu (2017)	Control	N/A	-	N/A	↑	Some Concerns
RCT	Yu (2017)	Experimental	N/A	-	N/A	↑	
Non-RCT	Alwhaibi (2020)	Experimental ^e	N/A	-	N/A	↑	Serious
Non-RCT	Alwhaibi (2020)	Experimental ^f	N/A	-	N/A	↑	
Non-RCT	Liu (2014b)	Control	N/A	↑	-	N/A	Unclear
Non-RCT	Liu (2014b)	Experimental	N/A	↑	↑	N/A	
Non-RCT	Patel (2019)	Control	N/A	↑	↑	↑	Serious
Non-RCT	Patel (2019)	Experimental	N/A	↑	↑	↑	

Non-RCT	Rickards (2012)	Control	-	N/A	N/A	-	Serious
Non-RCT	Rickards (2012)	Experimental	-	N/A	N/A	-	
Non-RCT	Saleh (2017)	Control	N/A	-	N/A	↑	Unclear
Non-RCT	Saleh (2017)	Experimental	N/A	↑	N/A	-	
Non-RCT	Sawaki (2014)	Control	N/A	-	N/A	-	Low
Non-RCT	Sawaki (2014)	Experimental	N/A	-	N/A	↑	
SG	Amengual (2013)	Experimental	N/A	↑	N/A	-	Serious
SG	Barker (2012)	Experimental	N/A	-	N/A	-	Low
SG	Bhasin (2012)	Experimental	N/A	↑	↑	N/A	Serious
SG	Brunetti (2015)	Experimental	N/A	↑	-	N/A	Serious
SG	Buick (2016)	Experimental	N/A	-	↑	↑	Serious
SG	Calabrò (2016)	Experimental	N/A	↑	↑	N/A	Serious
SG	Fujiwara (2015)	Experimental	N/A	-	↑	↑	Unclear
SG	Fujiwara (2009)	Experimental	N/A	-	↑	N/A	Critical
SG	Hara (2013)	Experimental	N/A	↑	↑	N/A	Unclear
SG	Horn (2016)	Experimental	N/A	↑	N/A	↑	Critical

SG	Kanenko (2019)	Experimental	N/A	↑	-	-	Unclear
SG	Khan (2020)	Experimental	N/A	↑	-	N/A	Unclear
SG	Könönen (2005)	Experimental	N/A	-	N/A	↑	Low
SG	Könönen (2012)	Experimental	N/A	↑	N/A	↑	Unclear
SG	Liepert (2006)	Experimental	N/A	↑	N/A	↑	Unclear
SG	Liepert (2000)	Experimental	N/A	↑	N/A	↑	Unclear
SG	Mattos (2021)	Experimental	-	N/A	N/A	-	Serious
SG	Page (2009)	Experimental	N/A	↑	-	-	Serious
SG	Pundik (2015)	Experimental	N/A	↑	N/A	-	Unclear
SG	Quinlan (2018)	Experimental	-	↑	-	N/A	Serious
SG	Ripollés (2016)	Experimental	N/A	↑	N/A	-	Serious
SG	Tarkka (2008)	Experimental	N/A	↑	N/A	↑	Serious
SG	Yarossi (2019)	Experimental	N/A	-	↑	↑	Serious
SG	Zhao (2012)	Experimental	N/A	↑	N/A	↑	Critical
RCT = Randomised Controlled Trial; Non-RCT = Non-Randomised Controlled Trial; SG = Single Group; a = tracking training; b = combination group; c = bobath; d = BASIS training; e = right hand trained; f = left hand trained; N/A = not							

applicable/not reported; ↑(green) = improved; - (yellow) = no change; ↓(red) = regressed. Low, Some Concerns and High = ROB-2 for RCT; Low, Unclear, Serious and Critical = ROBINS-I for Non-RCT and SG.

Intervention Element of Demographics and its Dimensions

Both demographics dimensions (recovery phase and severity) were reported in 102 intervention groups (96%). Four intervention groups did not report their participant's time since stroke.

Intervention Element of Type and its Dimensions

All four dimensions of type were reported in 12 intervention groups (11%), 45 intervention groups (42%) reported three dimensions, and 32 intervention groups (31%) reported two dimensions. Seventeen intervention groups (16%) reported only type of intervention. Repetitive task training ($n=24$) and CIMT ($n=15$) were the most common intervention types. The most common setting for therapy delivery was centre-based outpatient ($n=35$) and most frequently reported mode of delivery was face-to-face ($n=55$).

Intervention Element of Quality and its Dimensions

All three dimensions of quality were reported by seven intervention groups (7%), 19 intervention groups (18%) reported two dimensions, and 43 intervention groups (41%) reported one dimension. Thirty-seven intervention groups (35%) did not report any dimension of quality.

Intervention element of dose and its dimensions

No intervention group reported all seven dimensions of dose due to no intervention group reporting intensity. Six dimensions of dose were reported in 40 intervention groups (38%), and a further 19 intervention groups (18%) reported five dimensions.

Examination of Motor Interventions as a System

Three scenarios were examined: seven interventions groups were included in the restitution scenario; 11 intervention groups in the unchanged scenario; and remaining 86

intervention groups were included in the mixed scenario. Pooling each scenario's reported dimensions was used to create a signature for each scenario, represented in Figure 2.

In the restitution scenario, the interventions (systems) were most frequently conducted face-to-face (86%) in an inpatient setting (71%) with moderate or severely impaired, non-chronic (<6 months) stroke survivors (Figure 2a). There were no other distinct differences in the restitution scenario signature compared to the signature of the combined (mixed and unchanged scenarios). Breaking down the mixed and unchanged into two separate scenarios demonstrated that graded difficulty was infrequently used as a dimension (18%) in the unchanged scenario compared to the signature of the restitution scenario (71%) see Figure 2b. There was no one element or dimension that consistently delivered an improvement in biomarkers or clinical measures for stroke survivors across all scenarios.

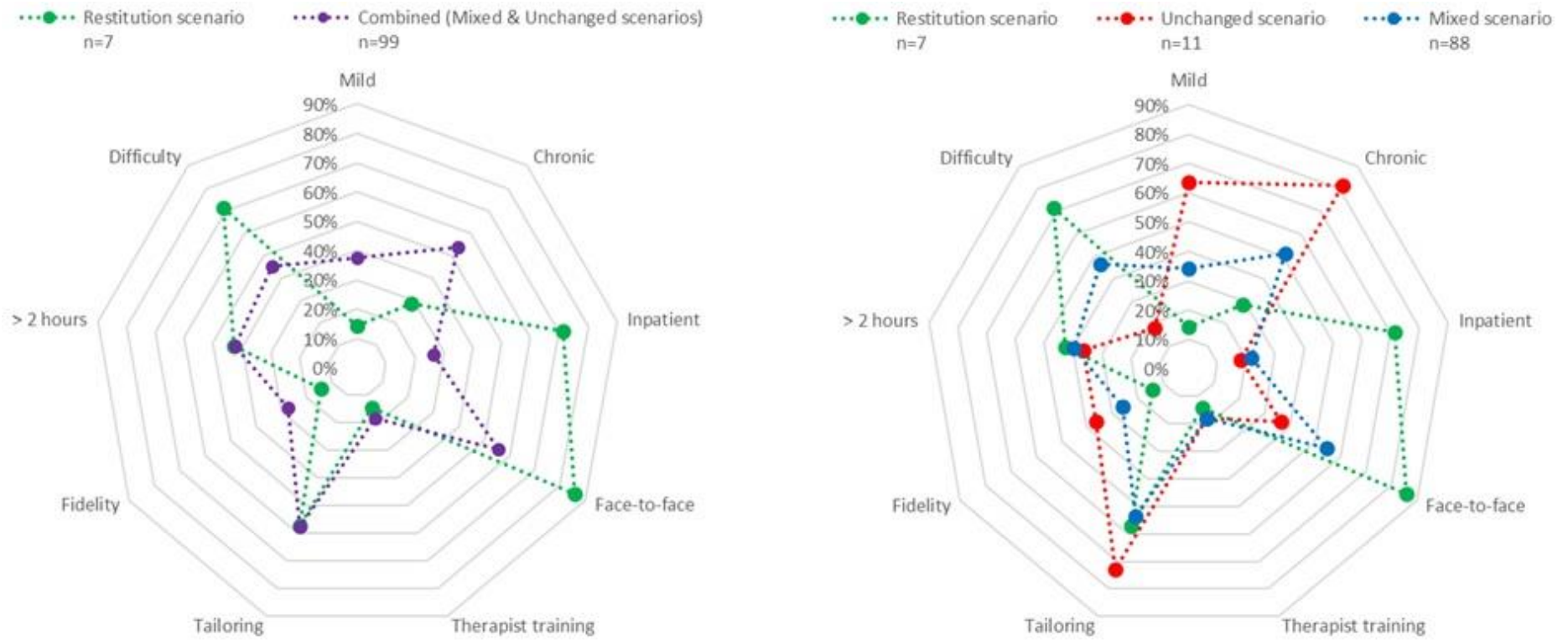


Figure 2: Signature of scenario signatures **A.** Restitution scenario vs Combined scenario **B.** Restitution scenario vs Unchanged scenario vs Mixed scenario.

Data is presented as a percentage of the total number of intervention groups included in the analysis (indicated by the legend) for each corresponding category. All data is dichotomous and presented with the affirmative contributing to a higher percentage and subsequently

indicated by the data point being further towards the edge of the radar plot (100%). Absence of data, data indicating no effect, or data indicating regression all are dichotomised to a negative result on these radar plots.

Discussion

We aimed to examine multidimensional elements of UL motor interventions using a systems paradigm and identify their influence on biomarkers and clinical measures after stroke. At a macroscopic level, the restitution scenario included interventions that more frequently reported graded difficulty, were delivered face-to-face, and were delivered in an inpatient setting. The restitution scenario also included more moderate to severely impaired stroke survivors in the first six months of recovery. Further, an important finding at the level of intervention groups was that no intervention group demonstrated a regression on either an impairment or activity measure. Interestingly, 26 of the intervention groups with participants in the chronic phase of recovery (47%) demonstrated improvement in either an impairment or activity measure. These results support the notion that UL motor intervention can facilitate improvement, even in the chronic phase of stroke recovery.

The restitution scenario included mostly moderate to severely impaired intervention groups which may have allowed for more scope to improve on a given clinical measure. In contrast, mildly impaired stroke survivors, who were more commonly included in the unchanged scenario, may have had less capacity to improve on a given clinical measure due to possible ceiling effects. This may have impacted our ability to index a MCID for the purpose of this review. The restitution scenario also included more stroke survivors who were in earlier phases of recovery (<six months), which suggests their outcome may have been supported by spontaneous biological recovery⁶. A time sensitive window of heightened potential for recovery is considered to last three to six months post stroke⁵. In this early period, the brain may be better able to capitalise on therapeutic opportunities⁴¹. Together, this highlights that UL intervention trials need to carefully consider who is recruited; that is, identifying important demographic data, both in severity and phase of recovery, as an element that may impact restitution.

Our analysis highlighted that there was more to a successful UL intervention than a single element, such as type, dose, or quality. The nuances of these results need to be carefully examined. Reporting of intervention dimensions was generally poor and with this volume of missing data, omission of measurement must not be mistaken for absence of effect. Until studies consistently report interventions using tools such as the TIDieR checklist¹⁵, the field may continue to struggle to translate findings into clinical practice. Interestingly, there was no treatment type that was represented more than another in the restitution scenario. Additionally, a consistent amount of therapist training (quality), tailoring of interventions (quality), and therapy per day (dose) was reported across scenarios. Multiple other dimensions (progressive difficulty, inpatient setting, and face-to-face delivery) were more prevalent in the restitution scenario compared to the unchanged scenario. The novelty of the current analysis, which is embedded within a systems paradigm, is the appreciation that restitution may be an *emergent property* of the combination of intervention elements and dimensions. In this systems paradigm, omission of an element or dimension may not simply reduce the magnitude of effect, it may change the outcome altogether and prevent the *emergence* of restitution. As exemplified above: even with adequate attention to the elements of dose, type, and quality of the intervention, inattention to the demographic element may see restitution not be realized. Considering multiple intervention elements essential to the design and operation of an intervention is in keeping with a recent trend in UL intervention studies that deliver improved clinical measures when conceptualized this way⁴². If interventions designed in a systems paradigm deliver clinical improvements to patients, therapists and researchers may equally benefit from this conceptual shift.

A second novel feature of this systematic review was the inclusion of clinical measures across multiple domains of the WHO-ICF in parallel with biomarkers. Our findings demonstrate the utility of this line of inquiry and support the need to prioritise collection of

biomarkers and clinical measures across multiple UL motor domains of the ICF in future research¹¹. Inclusion of biomarkers is key to help clarify *how* and *why* an intervention works by inferring what biological processes underpin the observed motor changes. Impairment and activity measures together provide more robust evidence for recovery than either one measure used in isolation. When improvement in a clinical measure was demonstrated, this review found that there was often a disconnect with improvements in biomarkers. This highlights the importance of selecting the right biomarker and clinical measures for the right population. For example: transcranial magnetic stimulation relies on intact corticospinal tract architecture, which is often compromised in more severely impaired stroke survivors⁴³; and timed clinical measures (e.g., box and block test) may more appropriately interrogate change in more mild populations as ordinal clinical measures (e.g., motor assessment scale) are more prone to ceiling effects⁴⁴. Inclusion of kinematic measures would further advance the discussion of restitution and extend the findings of this review. While clinical measures are useful and easily accessible to monitor change, they cannot fully appreciate if recovery was achieved through compensation or restitution⁴⁵. Kinematic measures have potential to discern between these two outcomes. Researchers have acknowledged the need to develop efficient and reliable methods for kinematic data collection and embed these measures within UL trials, and this remains a high priority⁴⁵.

This review has some limitations. Only studies with >10 participants were included. This may have led to exclusion of studies with small numbers reporting new or emerging interventions. However, small under-powered studies would have likely been rated at high RoB. Limiting to English excluded studies in other languages. The use of a 20% MCID for studies with an undocumented MCID led to a higher standard than historically applied⁴⁶. However, this threshold is a cautious interpretation that is within the range of 16%-30% defined for other outcomes included in this review³⁷. Interestingly, no reported results would

have changed if a 10% threshold had been applied. Dichotomising intervention dimensions reduces the nuance of the findings. Omission of measurement is not absence of effect and caution must be taken when interpreting these results (i.e., Figure 2a and 2b). The routine use of established tools in UL trials may improve reporting of our interventions and advance our understanding of the impact that motor interventions have on recovery⁴⁷. Finally, it is important to note that none of the studies included in this review intended their results to be examined in a systems paradigm, or for their outcomes to be presented this way. This limits the strength of the findings in this review as studies may have chosen to omit or emphasise certain aspects of their findings in the publication process.

Conclusion

A systems paradigm may be one of many approaches to understand UL motor restitution. This is in keeping with the finding that no single element of a motor intervention consistently led to improvements in biomarkers, impairment, or activity measures in the examined intervention groups. Given the difficulties with dramatically improving recovery profiles from UL motor intervention, different approaches should be explored to drive the field of stroke recovery forward in its thinking. While this review demonstrated that motor interventions can be conceptualized in a systems paradigm, it does not suggest that the proposed dimensions and elements are complete. Some elements were not able to be considered in our analysis, such as motivation, and these should be considered in future work. Careful selection of participants, intervention elements, clinical measures and biomarkers remain not only key considerations but also key tools that may progress the field closer to understanding UL restitution.

Disclosures:

Independent contractor work outside submitted work: AB, Biogen.

Funding:

Person: National Health and Medical Research Council of Australia [KSH:1088449]; Heart Foundation of Australia [AB:GNT100784, GNT104748]. Institutional: Florey Institute of Neuroscience and Mental Health acknowledges the Victorian Government's Operational Infrastructure Support Grant [KSH/AB].

Data availability: Upon reasonable request to kate.hayward@unimelb.edu.au.

Supplemental materials:

Supplemental I: Electronic database search strategy for all databases used

Supplemental II: Risk of bias ratings of included RCTs: biomarkers and clinical outcomes

Supplemental III: Risk of bias ratings of Non-RCTs: biomarkers and clinical outcomes

Supplemental IV: Data extraction form explanation

Supplemental V: Classification of severity

Supplemental VI: Summary of upper limb clinical measures

Supplemental VII: PRISMA Flow of included studies

Supplemental VIII: Studies excluded at full text

Supplemental IX: Summary of included studies

Supplemental X: References for included studies

References

1. Pollock A, St George B, Fenton M, Firkins L. Top 10 research priorities relating to life after stroke—consensus from stroke survivors, caregivers, and health professionals. *International Journal of Stroke*. 2014;9(3):313-320.
2. Lannin N, Ada L, Lindley R, Longworth M, McCluskey A, Middleton S. Stroke clinicians' priorities for stroke research. 2012;
3. Simpson LA, Hayward KS, McPeake M, Field TS, Eng JJ. Challenges of Estimating Accurate Prevalence of Arm Weakness Early After Stroke. *Neurorehabilitation and Neural Repair*. 2021
4. Smith WS, Sung G, Starkman S, et al. Safety and efficacy of mechanical embolectomy in acute ischemic stroke: results of the MERCI trial. *Stroke*. 2005;36(7):1432-1438.
5. Nakayama H, Jørgensen HS, Raaschou HO, Olsen TS. Recovery of upper extremity function in stroke patients: the Copenhagen Stroke Study. *Archives of physical medicine and rehabilitation*. 1994;75(4):394-398.
6. Bernhardt J, Hayward KS, Kwakkel G, et al. Agreed definitions and a shared vision for new standards in stroke recovery research: the stroke recovery and rehabilitation roundtable taskforce. *International Journal of Stroke*. 2017;12(5):444-450.
7. Boyd LA, Hayward KS, Ward NS, et al. Biomarkers of stroke recovery: consensus-based core recommendations from the stroke recovery and rehabilitation roundtable. *International Journal of Stroke*. 2017;12(5):480-493.
8. Organization WH. International Classification of Functioning, Disability, and Health: ICF.
9. Organization WH. Towards a Common Language for Functioning, Disability and Health ICF. 2002
10. Pascual-Leone A, Amedi A, Fregni F, Merabet LB. The plastic human brain cortex. *Annu Rev Neurosci*. 2005;28:377-401.
11. Kwakkel G, Lannin NA, Borschmann K, et al. Standardized measurement of sensorimotor recovery in stroke trials: consensus-based core recommendations from the stroke recovery and rehabilitation roundtable. *Neurorehabilitation and neural repair*. 2017;31(9):784-792.
12. Campbell M, Fitzpatrick R, Haines A, et al. Framework for design and evaluation of complex interventions to improve health. *Bmj*. 2000;321(7262):694-696.
13. Datta J, Petticrew M. Challenges to evaluating complex interventions: a content analysis of published papers. *BMC public health*. 2013;13(1):1-18.
14. Anderson LM, Petticrew M, Chandler J, et al. Introducing a series of methodological articles on considering complexity in systematic reviews of interventions. *Journal of clinical epidemiology*. 2013;66(11):1205-1208.
15. Hoffmann TC, Glasziou PP, Boutron I, et al. Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. *Bmj*. 2014.
16. Buchbinder BB, Bennell K, Brosseau L, et al. Consensus on Exercise Reporting Template (CERT). 2016.
17. Hayward KS, Churilov L, Dalton EJ, et al. Advancing Stroke Recovery Through Improved Articulation of Nonpharmacological Intervention Dose. *Stroke*. 2021.
18. Hayward KS, Brauer SG. Dose of arm activity training during acute and subacute rehabilitation post stroke: a systematic review of the literature. *Clinical rehabilitation*. 2015;29(12):1234-1243.
19. Pollock A, Farmer SE, Brady MC, et al. Interventions for improving upper limb function after stroke. *Cochrane Database of Systematic Reviews*. 2014.
20. van der Vliet R, Selles RW, Andrinopoulou ER, et al. Predicting upper limb motor impairment recovery after stroke: a mixture model. *Annals of neurology*. 2020;87(3):383-393.
21. Von Bertalanffy L. An outline of general system theory. *British Journal for the Philosophy of science*. 1950;
22. Vemuri V. *Modeling of complex systems: an introduction*. Academic Press; 2014.

23. May C. A rational model for assessing and evaluating complex interventions in health care. *BMC health services research*. 2006; 6(1):1-11.
24. Richards DA, Hallberg IR. Complex interventions in health: an overview of research methods. 2015.
25. Australian-Stroke-Foundation. The Economic Impact of Stroke in Australia. Deloitte Access Economics; 2020. November, 2020. Department of Health.
26. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71.
27. Innovation VH. Covidence systematic review software.
28. Lin I-H, Tsai H-T, Wang C-Y, Hsu C-Y, Liou T-H, Lin Y-N. Effectiveness and superiority of rehabilitative treatments in enhancing motor recovery within 6 months poststroke: a systemic review. *Archives of Physical Medicine and Rehabilitation*. 2019;100(2):366-378.
29. Sterne JA, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *bmj*. 2019;366
30. Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *bmj*. 2016;355
31. Wolf SL, Lecraw DE, Barton LA, Jann BB. Forced use of hemiplegic upper extremities to reverse the effect of learned nonuse among chronic stroke and head-injured patients. *Experimental neurology*. 1989;104(2):125-132.
32. Nijland RH, Van Wegen EE, Harmeling-van der Wel BC, Kwakkel G, Investigators EPoFOAS. Accuracy of physical therapists' early predictions of upper-limb function in hospital stroke units: the EPOS Study. *Physical therapy*. 2013;93(4):460-469.
33. Buma FE, Lindeman E, Ramsey NF, Kwakkel G. Functional neuroimaging studies of early upper limb recovery after stroke: a systematic review of the literature. *Neurorehabilitation and neural repair*. 2010;24(7):589-608.
34. Burke Quinlan E, Dodakian L, See J, et al. Neural function, injury, and stroke subtype predict treatment gains after stroke. Research Support, N.I.H., Extramural. *Annals of Neurology*. 2015;77(1):132-45.
35. Pundik S, McCabe JP, Hrovat K, et al. Recovery of post stroke proximal arm function, driven by complex neuroplastic bilateral brain activation patterns and predicted by baseline motor dysfunction severity. *Front Hum Neurosci*. 2015;9:394.
36. Metcalf C, Adams J, Burrige J, Yule V, Chappell P. A review of clinical upper limb assessments within the framework of the WHO ICF. *Musculoskeletal Care*. 2007;5(3):160-173.
37. Lang CE, Edwards DF, Birkenmeier RL, Dromerick AW. Estimating minimal clinically important differences of upper-extremity measures early after stroke. *Archives of physical medicine and rehabilitation*. 2008;89(9):1693-1700.
38. Schneider EJ, Lannin NA, Ada L, Schmidt J. Increasing the amount of usual rehabilitation improves activity after stroke: a systematic review. *Journal of physiotherapy*. 2016;62(4):182-187.
39. Lin KC, Chung HY, Wu CY, et al. Constraint-induced therapy versus control intervention in patients with stroke: a functional magnetic resonance imaging study. *Am J Phys Med Rehabil*. Mar 2010;89(3):177-85.
40. Li F, Zhang T, Li BJ, Zhang W, Zhao J, Song LP. Motor imagery training induces changes in brain neural networks in stroke patients. *Neural Regen Res*. Oct 2018;13(10):1771-1781.
41. Dromerick AW, Geed S, Barth J, et al. Critical Period After Stroke Study (CPASS): A phase II clinical trial testing an optimal time for motor recovery after stroke in humans. *Proceedings of the National Academy of Sciences*. 2021;118(39)
42. Ward NS, Brander F, Kelly K. Intensive upper limb neurorehabilitation in chronic stroke: outcomes from the Queen Square programme. *Journal of Neurology, Neurosurgery & Psychiatry*. 2019;90(5):498-506.

43. Stinear CM, Byblow WD, Ackerley SJ, Smith MC, Borges VM, Barber PA. PREP2: A biomarker-based algorithm for predicting upper limb function after stroke. *Annals of clinical and translational neurology*. 2017;4(11):811-820.
44. Hayward KS, Kramer SF, Thijs V, et al. A systematic review protocol of timing, efficacy and cost effectiveness of upper limb therapy for motor recovery post-stroke. *Systematic reviews*. 2019;8(1):1-8.
45. Kwakkel G, Van Wegen E, Burridge J, et al. Standardized measurement of quality of upper limb movement after stroke: consensus-based core recommendations from the second stroke recovery and rehabilitation roundtable. *Neurorehabilitation and neural repair*. 2019;33(11):951-958.
46. Van der Lee JH, Wagenaar RC, Lankhorst GJ, Vogelaar TW, Devillé WL, Bouter LM. Forced use of the upper extremity in chronic stroke patients: results from a single-blind randomized clinical trial. *Stroke*. 1999;30(11):2369-2375.
47. Walker MF, Hoffmann TC, Brady MC, et al. Improving the development, monitoring and reporting of stroke rehabilitation research: consensus-based core recommendations from the stroke recovery and rehabilitation roundtable. *International Journal of Stroke*. 2017;12(5):472-479.