Supplemental file to:

A stroke recovery trial development framework: Consensus-based core recommendations from the Second Stroke Recovery and Rehabilitation Roundtable

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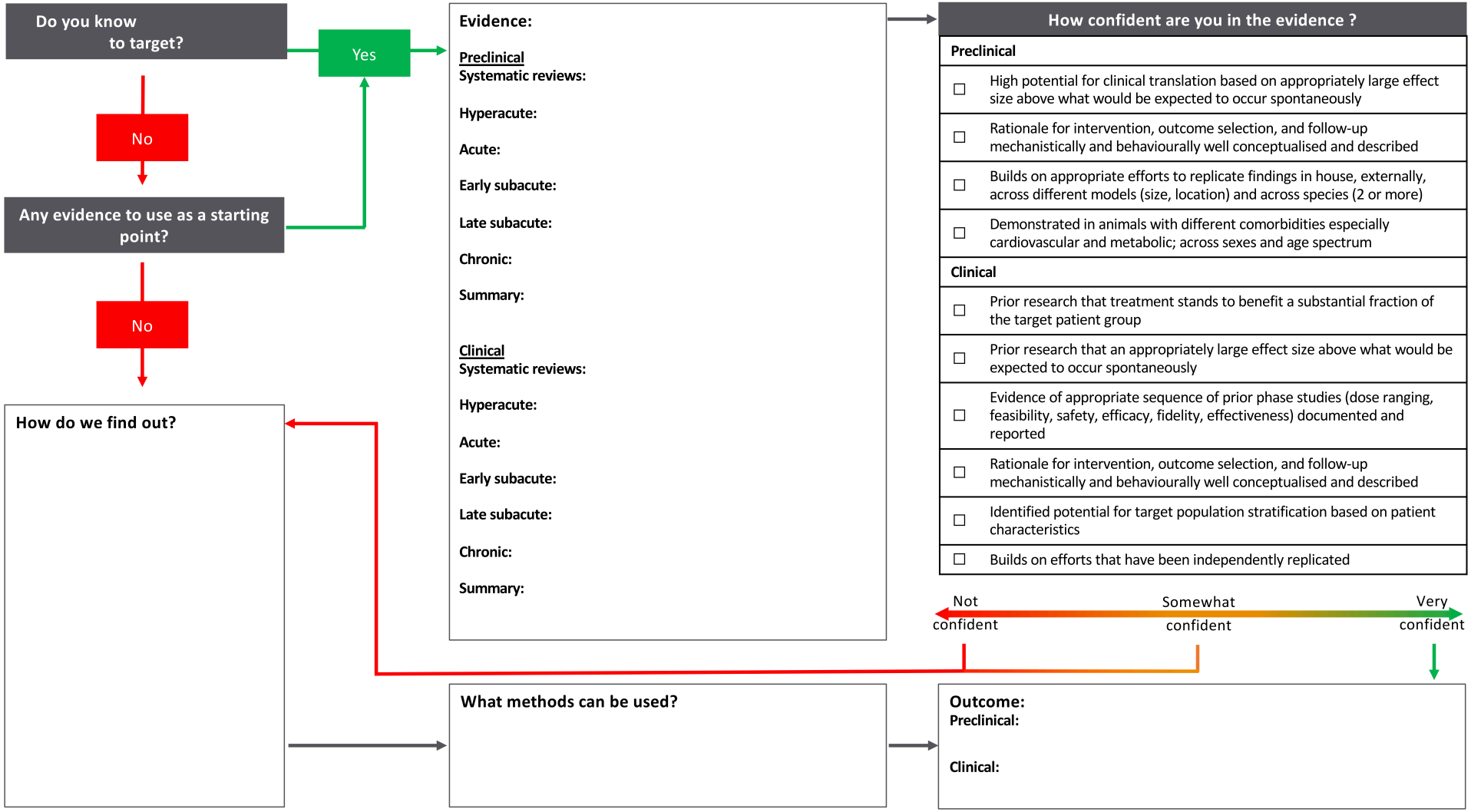
Supplemental Files:

Supplemental 1: Blank SRRR-TDF

Supplemental 2: Summary of issues raised by research to date across the knowledge units. **A:** HOW MUCH. **B:** WHAT. **C:** WHO. **D:** WHEN. **E:** ADJUVANTS.

Supplemental 3: Supporting reference list for Figure 3. **A:** HOW MUCH. **B:** WHAT. **C:** WHO. **D:** WHEN. **E:** ADJUVANTS.

Supplemental 1: Blank Stroke Recovery and Rehabilitation Roundtable Trials Development Framework (SRRR-TDF)



Supplemental 2: Summary of issues raised by research to date across the knowledge units.

A. HOW MUCH[1]

Characteristics of research to date: Clinical	Characteristics of research to date: Preclinical	Gap for research and priority for funding	Strategies to advance understanding of issue
• Research to date reports dose as "intended" and/or "time scheduled for therapy" as a proxy for dose. Lack of details of "actual dose" including number of repetitions and active time on task. For further explanation of this issue, see (1). • Need proportional increase reported for trials - not just amounts (trialists to date rarely considered dose difference between control and higher dose groups). • Work to date limited by trials who claim to test HOW MUCH but vary WHAT between groups, and by trials who claim to test HOW MUCH but have wide variability in WHO. • Few trials have considered WHAT alongside HOW MUCH – most do *not* deliver high-challenge, meaningful, high-repetition task training. In fact, most fail to provide sufficient explanation to complete a TIDieR checklist (2). • Clear description of control/usual therapy comparison necessary (see Lohse et al (3). • An additional 120minutes per day, 5 days per week (compared to 60 minutes per day 5 days per week) is the largest	• Three preclinical studies address issue of dose (8-10). All support importance of dose, particularly if individually tailored. • Effective animal reaching doses are much higher than human doses; ranging from 100-600 per session e.g., (9, 11). • Animal work suggests clear evidence of a threshold that is higher than doses in clinical studies. • HOW MUCH is not always clear. Measures are duration of session or amount of food consumed, do not always know number of reaches, successful and unsuccessful reaches except in single pellet studies. • Most preclinical studies in rodents do not incorporate a progressive challenge over time; task difficulty remains constant. • In contrast, non-human primate studies typically use a performance criterion to progressively challenge task (e.g., move to more difficult	• Need well-powered dose escalation/finding/response studies (not single group studies) in context of WHEN using confirmed WHAT delivered in confirmed WHO group(s) across preclinical and clinical population. • Need trials that test only HOW MUCH holding WHAT and WHO constant. • Need to understand the half-life of motor training interventions (to guide frequency decisions). Preclinical can advance this gap. • Need to understand potential harms of large doses in clinical populations. • Frequency of rehabilitation sessions should be explored for efficacy; multiple short sessions distributed through day versus long single session, i.e., schedule is also important to understand and optimise. • Need to understand how transferrable the preclinical data are to clinical trials (e.g., lesion differences between preclinical and clinical trials). Also, preclinical can vary HOW MUCH and WHO (e.g., lesion location/severity) within same study, which is not easily possible in clinical studies. • Preclinical studies should incorporate at least two reaching outcome measures	See "How do we find out" and "What methods can we use" *boxes* in Figure x for overview. In addition the following points may need to be considered: • Operational definition of dose and agreement on how this will be reported in all future trials required (TIDieR (2)). We need number of repetitions over time, frequency and time on active task all recorded, with agreement on how repetitions of functional activities will be recorded. • Upper limb trials need to focus on achieving higher training doses (14, 15), as lower doses have already been tested and are likely to be subtherapeutic.

additional dose tested (4); other trials are substantially lower. • VECTORS trial (5) reported that 3 h per day of constraint induced movement therapy (CIMT) compared to 2 h per day, led to worse motor outcomes as measured by the Action Research Arm Test (ARAT) (note, pilot, so no power calculation) – suggests need to understand potential *harm* of larger doses of motor training of the upper limb. • Effect of HOW MUCH measured in research using outcome tools of ARAT (most common), Wolf Motor Function Test (WMFT), then Fugl Meyer Upper Extremity (FMUE); few kinematics. See elsewhere (6, 7) for discussion of potential outcome tools.	when 500 successful trials in one session obtained) (12, 13). • No exploration of the optimal dose to increase recovery (i.e. number of repetition or time of training) across rodent and non-human primate stroke models. • Like clinical studies, preclinical research rarely considers WHAT or WHO in context of HOW MUCH. • Preclinical studies often use same task (e.g. single pellet) for training and assessment, which likely biases towards larger effect size.	e.g., single pellet & staircase. Clinical studies should incorporate impairment, activity (7) and kinematics (see [Kwakkel KIN paper for review]).	

[1] It should be noted that the emphasis of our group was on comparative effectiveness trials targeting stroke recovery. We recognise that there is some evidence that demonstrates promise within a given knowledge unit that we have not included e.g., doses as high as 300 hours over 10 weeks (16, 17) and 90 hours over 3 weeks (18) have been tested, but as they have not compared different doses they have not been used to inform our decision concerning HOW MUCH.

B. WHAT

Characteristics of research to date: Clinical	Characteristics of research to date: Preclinical	Gap for research and priority for funding	Strategies to advance understanding of issue
• Common upper limb behavioural treatment trials have focused on constraint induced movement therapy (CIMT), task specific and repetitive task training (RTT) and robotics (19) usually compared to usual care (which in itself is poorly defined) (20). • Of these, moderate-quality evidence for a beneficial effect of CIMT and a relatively high dose of repetitive task practice in comparison to standard or matched treatment (19). • Both CIMT and RTT stress that simple repetition alone is ineffective. Both benefit from some form of instruction as well as the transfer of new skills to activities of daily living (21). • Successful post-stroke recovery is likely to require more than one component, or 'active ingredient' (22). A few studies have investigated more complex interventions (23), which means an intervention involving several potentially interacting elements or components, e.g., (24) but more are required. • There is insufficient data to reveal the relative effectiveness of different types of interventions through direct comparison. • Little focus on accurately measuring and understanding quality of movement,	• In some intervention trials, some active ingredients (intensive and repetitive) have been defined. In some trials interventions that may translate to clinical setting e.g., enriched environment plus repetitive reaching training, have been tested (9). • Rehabilitation approaches tested are limited. They have either consisted of enriched environment (rodent); the repetition of precision grasps with or without increasing the difficulty (both rodent and non-human primate). No studies have looked at the effects of the combination of various movements or tasks (e.g. force versus skill, combining complex reaches with grasp, unimanual versus bimanual, etc) or how they could promote different mechanisms of recovery in the brain.	• Research to inform understanding of the active ingredients, with consideration of WHO and WHEN, and providing threshold dose of HOW MUCH should be prioritised over more 'pragmatic' research approaches. • We should target interventions with a high level of efficacy (achieving MCID or higher) and then begin to work out how to optimise the intervention, including WHO and WHEN. • Currently, outcome measures do not have the granularity to help understand the effect of interventions on key aspects of the recovery process e.g., behavioural repair vs compensation (7). See Kwakkel et al., [SRRR2 paper] for a full summary. • Clear rationale for intervention needs to be defined and embedded within TIDieR (2)/SRRR 1 (25), with consideration of complex intervention guidelines e.g., MRC (23).	See "How do we find out" and "What methods can we use" *boxes* in Figure x for overview. In addition the following points may need to be considered: • Successful post-stroke rehabilitation is likely to be a complex intervention and so investigating single elements is unlikely to be successful. • We need to start with an informed HOW MUCH of interventions (i.e., greater than MCID effect such as McCabe (16), Ward (18)), for greatest opportunity to learn about active ingredients of effective interventions. • Identifying active ingredients will be achieved through careful assessment of the nature of the behavioural intervention and of the resulting behavioural change at a level of fine-grained detail (e.g. kinematic assessment in the motor domain) that is not currently undertaken on a regular basis. • If possible, learning how key elements of an intervention influence different aspects of the resulting behavioural change (e.g. impairment, activity, participation,

including importance of having shoulder function to place hand in context.			as well as generalisation, and retention/half-life) in different populations (WHO) would advance the field and lead to more carefully targeted treatments.

C. WHO

Characteristics of research to date: Clinical	Characteristics of research to date: Preclinical	Gap for research and priority for funding	Strategies to advance understanding of issue
• Behavioural phenotype measured via bedside exam is a weak marker for the underlying biological state of the brain (26). • Patients are not usually selected for trials based on a measurement that is aligned with the biology of the behavioural training intervention. In some trials, stratification has been based on e.g., presence/absence of voluntary finger extension (27). • Clinical studies have generally not stratified or tested whether an intervention has different effects depending on injury severity or biomarker status e.g., MEP using TMS. • There are few instances of brain assessment biomarkers being used in clinical trials to successfully select enrolees to identify responders. • Clinical populations demonstrate variability in response to therapy e.g., (28). Inherent variability is often not analyzed to give insights into individual responses to the intervention. • Most clinical studies target stroke survivors with mild to moderate impairments. However, emerging data suggesting that there is a bimodal distribution of upper limb impairment; predominant subgroups have little to no impairment or severe impairment (29).	• Very few preclinical studies specifically test whether an intervention (e.g. rehabilitation, drugs, etc.) has different effects depending on injury severity (i.e. small, medium, large infarcts) and/or varying degrees of initial impairment. • Animal models, even when targeting a specific brain region (e.g. caudal forelimb area, CFA), result in considerable variability in response (30). Inherent variability is often not analyzed to give insights into individual responses to the intervention. • Most preclinical investigators working across rodent and non-human primate models target the forelimb motor cortex, even though subcortical injury is commonly seen clinically. • In carefully controlled studies, training improves recovery in both moderate and severe stroke (based on infarct size, location and level of initial impairment).	• Hypothesis-driven studies of brain assessments to develop an approach that allows tailored selection of patients for interventions should be fostered and promoted across preclinical and clinical populations. • We need to further test proposed stratification approaches in comparative effectiveness recovery trials, such as stratifying in human trials using upper limb severity baseline Fugl Meyer, finger extension, Shoulder Abduction and Finger Extension (SAFE) scores, motor evoked potential (MEP) status, degree of corticospinal tract injury, or models such as PREP (26, 31-34). • Research is needed to identify other reliable brain assessments that have been validated with respect to ability to distinguish biological subgroups, and ability to predict a substantial fraction of treatment response. Furthermore, validation across species would be advantageous. • The contributions of genetics and blood biomarkers is largely unexplored for its value in identifying WHO will respond to therapy and WHEN (26). • Validation of joint preclinical-clinical initiatives across centres and across models are needed. These efforts should take advantage of the complementary techniques and data collected in	See “How do we find out” and “What methods can we use” *boxes* in Figure x for overview. In addition the following points may need to be considered: • Establish a core data set of measures and timepoints of collection (i.e. motor outputs with certain fixed parameters; imaging; behavioural tests etc) that should be used across preclinical and clinical studies. Core outcomes have been identified for motor recovery trials in humans but this needs to be done in animal research. • We also need to develop and validate approaches to measuring the ‘success’ of a treatment that incorporates the degree of impairment (and other biological markers) of the patient at trial entry. • A big data study is needed using consistent measures and timepoints in a

		preclinical and clinical populations and use common outcome measures and biomarkers.	sufficiently large cohort to identify subgroups of patients within meaningful groups. • Preclinical and clinical researchers need to embrace idea of collecting big data in parallel to best inform clinical studies.

D. WHEN

Characteristics of research to date: Clinical	Characteristics of research to date: Preclinical	Gap for research and priority for funding	Strategies to advance understanding of issue
• Conceptual models of biological processes underling recovery post stroke, which could inform optimal intervention timing, lack strong evidence (35). • Decisions about WHEN to commence training often pragmatic rather than biologically informed (36, 37). • Majority of studies examine interventions commencing in the chronic phase (>6 months) of recovery (36, 38); only one pilot study (not powered) commenced within first 7-days post-stroke (39). • Timing, relative to stroke onset, often not clear (36, 40). • Timing window for inclusion often very wide (20), i.e., mechanism underlying observed improvement may be very different across the sample. • Rarely is time post stroke a prospective stratification variable or are analyses adjusted by time post stroke e.g., (41).	• Conceptual models of biological processes underlying recovery post stroke, which could inform optimal intervention timing, have moderate to strong evidence (42). • Mechanistic changes observed are matching well to recovery profiles (43-46). • The extent of the 'optimal window' or 'critical period' for delivering interventions with the potential to harness biological processes that support brain repair and recovery corresponds to ~5-30 days post-stroke. • Intervention trials are mainly conducted in the, acute (1-5/7days) and subacute (5/7days to 4-6wks) time windows, with few in the chronic phase (>2-3 months post stroke) (47). • Timing post stroke for inclusion often narrow (48). • Only a few studies have specifically looked at timing to start intervention (49-51).	• Research to inform understanding the biology (particularly molecular) of recovery (during and outside periods of spontaneous recovery), particularly related to the critical periods, is an urgent need. • Patient subgroups WHO recover at different rates and timing (recovery phenotypes) must be identified (see WHO) to inform clearer selection criteria and stratification for future trials. • We need to understand the interaction between WHEN and HOW MUCH, different doses may be required at different timepoints; and potentially WHO, as different people may benefit at different timepoints. • For trials of recovery interventions, clear justification for timing and tight(er) recruitment windows needed. • Develop biomarkers of rehabilitation readiness (an individual is in the optimal state for true recovery), future trials may be developed with a recruitment targeting individual readiness rather than time. These should start within the current best evidence window, not be pragmatically-driven.	• Identify timing variable(s) for stratification by conducting a large natural history, cohort study with detailed measurement at specific timepoints that are most critical for capturing change and reflect underlying biological processes – we need to use recovery outcomes that measure true recovery (movement quality and behaviour) and include candidate biomarkers. • Comparison of interventions (WHAT) in and outside of the hypothesised critical period needed. • Study designs that test potential biomarkers of rehabilitation readiness that include a sufficiently high dose (see above); this could be modelled across multiple domains e.g., speech, upper limb, gait.

E. ADJUVANTS

Characteristics of research to date: Clinical	Characteristics of research to date: Preclinical	Gap for research and priority for funding	Strategies to advance understanding of issue
• Studies are often small, with ADJUVANTS (brain stimulation (52-54), exercise pre-training to 'prime' the brain (55)) typically applied in the chronic phase of stroke recovery, usually for pragmatic rather than biologically-driven reasons. • Primary outcome is often poorly defined, with multiple outcomes addressed. • ADJUVANT(s) are often not paired with carefully developed and well-defined behavioural training of appropriate amount e.g., (56) (refer to HOW MUCH and WHAT for further details). • Larger, powered studies e.g., FOCUS (57), DARS (58) found no benefits when combined with with standard clinical care. Whether these trial outcomes would differ if combined with defined behavioural training is unknown.	• Most studies of ADJUVANTS have not combined treatment with rehabilitation. Therefore, the independent effects of behavioural training plus ADJUVANT(s) is largely unknown. • Many studies have treated in a very early time window (hyperacute/acute), therefore it is not possible to understand restorative vs. neuroprotective effects. • Models largely limited to cortical stroke; with few exceptions, see (59, 60). • Outcome measures are often non-translatable behavioural instruments e.g., cylinder tests, roto-rod, etc (42). • Stimulation is currently the most tested (across lab and across models) approach that could increase rehabilitation effects. But stimulations are all invasive. No study has looked at non-invasive stimulation and rehabilitation.	• Consideration of WHEN is the optimal time to intervene, combined with WHAT behavioural training and in whom (WHO), with a clear link to a neurobiological mechanism(s). • Most clinical studies are conducted in the chronic phase of recovery, which is opposite to the preclinical studies; better preclinical-clinical alignment required to improve translation. • ADJUVANTS need to be tested across different lesion profiles in preclinical research to advance understanding of WHO best to target. • Optimisation of brain stimulation parameters (onset time, location, duration, frequency, number of stimulation etc) that should then be applied consistently across trials. • Careful consideration of the phasing of research trials is required to inform progression to later stage investigations.	• Most promising approaches should be systematically explored across labs, models, lesion profiles prior to initiation of large-scale clinical trials. • For a given ADJUVANT, clinical studies should target the same time window that was shown to be effective in preclinical studies. In contrast, preclinical work can test phases most often targeted in clinical studies i.e., chronic. • Pairing of ADJUVANTS with behavioural interventions to optimise recovery needs careful consideration as part of trial development.

Supplemental 2 Tables A-E References

1. Lang CE, Strube MJ, Bland MD, Waddell KJ, Cherry-Allen KM, Nudo RJ, et al. Dose response of task-specific upper limb training in people at least 6 months poststroke: A phase II, single-blind, randomized, controlled trial. Annals of neurology. 2016;80:342-54.
2. Hoffmann TC, Glasziou PP, Boutron I, Milne R, Perera R, Moher D, et al. Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. Bmj. 2014;348:g1687.
3. Lohse KR, Pathania A, Wegman R, Boyd LA, Lang CE. On the Reporting of Experimental and Control Therapies in Stroke Rehabilitation Trials: A Systematic Review. Arch Phys Med Rehabil. 2018;99:1424-32.
4. Han C, Wang Q, Meng PP, Qi MZ. Effects of intensity of arm training on hemiplegic upper extremity motor recovery in stroke patients: a randomized controlled trial. Clin Rehabil. 2013;27:75-81.
5. Dromerick AW, Lang CE, Birkenmeier RL, Wagner JM, Miller JP, Videen TO, et al. Very Early Constraint-Induced Movement during Stroke Rehabilitation (VECTORS). A single-center RCT. Neurology. 2009;73:195-201.
6. Lang CE, Bland MD, Bailey RR, Schaefer SY, Birkenmeijer RL. Assessment of upper extremity impairment, function and activity after stroke: Foundations for clinical decision making. Journal of Hand Therapy. 2013;26:104-15.
7. Kwakkel G, Lannin N, Borschmann K, English C, Ali M, Churilov L, et al. Standardised measurement of sensorimotor recovery in stroke trials: consensus-based core recommendations from the Stroke Recovery and Rehabilitation Roundtable (SRRR). International Journal of Stroke. 2017;12:451-61.
8. MacLellan CL, Keough MB, Granter-Button S, Chernenko GA, Butt S, Corbett D. A critical threshold of rehabilitation involving brain-derived neurotrophic factor is required for poststroke recovery. Neurorehabil Neural Repair. 2011;25:740-8.
9. Jeffers MS, Corbett D. Synergistic Effects of Enriched Environment and Task-Specific Reach Training on Poststroke Recovery of Motor Function. Stroke. 2018;49:1496-503.
10. Bell JA, Wolke ML, Ortez RC, Jones TA, Kerr AL. Training intensity affects motor rehabilitation efficacy following unilateral ischemic insult of the sensorimotor cortex in C57BL/6 mice. Neurorehabilitation and Neural Repair.29:590-8.
11. Nudo RJ, Miliken GW. Reorganisation of movement representations in primary motor cortex following focal ischemic infarcts in adult squirrel monkeys. Journal of neurophysiology. 1996;75:144-9.
12. Nudo RJ, Milliken GW, Jenkins WM, Merzenich MM. Use dependent alterations of movement representations in primary motor cortex of adult squirrel monkeys. Journal of Neuroscience. 1996;16:785-807.
13. Murata YN, Higo N, Oishi T, Yamashita A, Matsuda K, Hayashi M, et al. Effects of motor training on the recovery of manual dexterity after primary motor cortex lesion in macaque monkeys. Journal of neurophysiology. 2008;99:773-86.
14. Schneider EJ, Lannin NA, Ada L, Schmidt J. Increasing the amount of usual rehabilitation improves activity after stroke: a systematic review. J Physiother. 2016;62:182-7.
15. Lohse KR, Lang CE, Boyd LA. Is more better? Using meta-data to explore dose-response relationships in stroke rehabilitation. Stroke. 2014;45:2053-8.
16. McCabe J, Monkiewicz M, Holcomb J, Pundik S, Daly JJ. Comparison of robotics, functional electrical stimulation, and motor learning methods for treatment of persistent upper extremity dysfunction after stroke: a randomized controlled trial. Arch Phys Med Rehabil. 2015;96:981-90.
17. Daly JJ, McCabe JP, Holcomb J, Monkiewicz M, Gansen J, Pundik S. Long-Dose Intensive Therapy Is Necessary for Strong, Clinically Significant, Upper Limb Functional Gains and Retained Gains in Severe/Moderate Chronic Stroke. Neurorehabil Neural Repair. 2019:1545968319846120.

18. Ward NS, Brander F, Kelly K. Intensive Upper Limb Neurorehabilitation in Chronic Stroke - The Queen Square Programme. Journal of Neurology, Neurosurgery, and Psychiatry. 2019;90:498-506.
19. Pollock A, Farmer SE, Brady MC, Langhorne P, Mead GE, Mehrholz J, et al. Interventions for improving upper limb function after stroke. The Cochrane database of systematic reviews. 2014;11:CD010820.
20. Lohse KR, Schaefer SY, Raikes AC, Boyd LA, Lang CE. Asking New Questions with Old Data: The Centralized Open-Access Rehabilitation Database for Stroke. Front Neurol. 2016;7:153.
21. Kwakkel G, Veerbeek JM, van Wegen EE, Wolf SL. Constraint-induced movement therapy after stroke. Lancet Neurol. 2015;14:224-34.
22. Lang CE, Lohse KR, Birkenmeijer RL. Dose and timing in neurorehabilitation: prescribing motor therapy after stroke. Current Opinions in Neurology. 2015;28:549-55.
23. Council MR. Developing and evaluating complex interventions. wwwmrcacuk/complexinterventionsguidance. 2006.
24. Winstein CJ, Wolf SL, Dromerick AW, Lane CJ, Nelsen MA, Lewthwaite R, et al. Effect of a Task-Oriented Rehabilitation Program on Upper Extremity Recovery Following Motor Stroke: The ICARE Randomized Clinical Trial. JAMA. 2016;315:571-81.
25. Walker MF, Hoffmann TC, Brady MC, Dean CM, Eng JJ, Farrin AJ, 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 : official journal of the International Stroke Society. 2017;12:472-9.
26. Boyd LA, Hayward KS, Ward NS, Stinear CM, Rosso C, Fisher RJ, et al. Biomarkers of stroke recovery: Consensus-based core recommendations from the Stroke Recovery and Rehabilitation Roundtable (SRRR). International Journal of Stroke. 2017;12:480-93.
27. Kwakkel G, Winters C, van Wegen EE, Nijland RH, van Kuijk AA, Visser-Meily A, et al. Effects of Unilateral Upper Limb Training in Two Distinct Prognostic Groups Early After Stroke: The EXPLICIT-Stroke Randomized Clinical Trial. Neurorehabil Neural Repair. 2016;30:804-16.
28. Nouri S, Cramer SC. Anatomy and physiology predict response to motor cortex stimulation after stroke. Neurology. 2011;77:1076-83.
29. Simpson L, Hayward KS, McPeake M, Eng JJ. An updated distribution of upper limb weakness post stroke: are fewer people experiencing arm weakness today? International Journal of Stroke. 2018;13:41.
30. Karthikeyan S, Jeffers MS, Carter A, Corbett D. Characterizing Spontaneous Motor Recovery Following Cortical and Subcortical Stroke in the Rat. Neurorehabil Neural Repair. 2019;33:27-37.
31. Winters C, Heymans MW, van Wegen EE, Kwakkel G. How to design clinical rehabilitation trials for the upper paretic limb early post stroke? Trials. 2016;17:468.
32. Cassidy JM, Tran G, Quinlan EB, Cramer SC. Neuroimaging Identifies Patients Most Likely to Respond to a Restorative Stroke Therapy. Stroke. 2018;49:433-8.
33. Stinear CM, Barber PA, Petoe M, Anwar S, Byblow WD. The PREP algorithm predicts potential for upper limb recovery after stroke. Brain. 2012;135:2527-35.
34. Stinear CM, Byblow WD, Ackerley SJ, Smith MC, Borges VM, Barber PA. PREP2: A biomarker-based algorithm for predicting upper limb function after stroke. Ann Clin Transl Neurol. 2017;4:811-20.
35. Bernhardt J, Hayward KS, Kwakkel G, Ward NS, Wolf SL, Borschmann K, 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;12:444-50.
36. Borschmann K, Hayward KS, Raffelt A, Churilov L, Kramer SF, Bernhardt JA. Rationale for intervention and dose is lacking in stroke recovery trials: A systematic review. Stroke research and treatment. 2018;8087372.
37. Winters C, Kwakkel G, van Wegen E, Nijland RH, Veerbeek JM, Meskers CG. Moving stroke rehabilitation forward: The need to change research. NeuroRehabilitation. 2018;43:19-30.

38. Stinear C, Ackerley S, Byblow W. Rehabilitation is initiated early after stroke, but most motor rehabilitation trials are not: a systematic review. Stroke. 2013;44:2039-45.
39. Hubbard IJ, Parsons MW, Neilson C, Carey LM. Task-specific training: evidence for and translation into clinical practice. Occupational Therapy International. 2009;16:175-89.
40. Ali M, English C, Bernhardt J, Sunnerhagen K, Brady M. More outcomes than trials: a call for consistent data collection across stroke rehabilitation trials. International Journal of Stroke.8:18-24.
41. Lang KC, Thompson PA, Wolf SL. The EXCITE trial: reacquiring upper-extremity task performance with early versus late deliv- ery of constraint therapy. Neurorehabilitation and Neural Repair. 2013;27:654-63.
42. Corbett D, Carmichael ST, Murphy TH, Jones TA, Schwab ME, Jolkkonen J, et al. Enhancing the Alignment of the Preclinical and Clinical Stroke Recovery Research Pipeline: Consensus-Based Core Recommendations From the Stroke Recovery and Rehabilitation Roundtable Translational Working Group. Neurorehabil Neural Repair. 2017;31:699-707.
43. Murphy TH, Corbett D. Plasticity during stroke recovery: from synapse to behaviour. Nature Reviews Neuroscience. 2009;10:861-72.
44. Carmichael ST. Emergent properties of neural repair: elemental biology to therapeutic concepts. Annals of neurology. 2016;79:895-906.
45. Carmichael ST, Archibeque I, Luke L, Nolan T, Momiy J, Li S. Growth-associated gene expression after stroke: evidence for a growth-promoting region in peri-infarct cortex. Exp Neurol. 2005;193:291-311.
46. Wahl AS, Omlor W, Rubio JC, Chen JL, Zheng H, Schroter A, et al. Neuronal repair. Asynchronous therapy restores motor control by rewiring of the rat corticospinal tract after stroke. Science. 2014;344:1250-5.
47. Janssen H, Speare S, Spratt NJ, Sena ES, Ada L, Hannan AJ, et al. Exploring the Efficacy of Constraint in Animal Models of Stroke: Meta-analysis and Systematic Review of the Current Evidence. Neurorehabilitation and Neural Repair. 2013;27:3-12.
48. Wahl AS, Schwab ME. Finding an optimal rehabilitation paradigm after stroke: enhancing fiber growth and training of the brain at the right moment. Frontiers in human neuroscience. 2014;8:381.
49. Biernaskie J, Chernenko G, Corbett D. Efficacy of rehabilitative experience declines with time after focal ischemic brain injury. Journal of Neuroscience. 2004;24:1245-54.
50. Barbay S, Plautz EJ, Friel KM, Frost SB, Dancause N, Stowe AM, et al. Behavioral and neurophysiological effects of delayed training following a small ischemic infarct in primary motor cortex of squirrel monkeys. Experimental Brain Research. 2006;169:106-16.
51. Hsu JE, Jones TA. Time-sensitive enhancement of motor learning with the less-affected forelimb after unilateral sensorimotor cortex lesions in rats. European Journal of Neuroscience. 2005;22:2069-80.
52. Simonetti D, Zollo L, Milighetti S, Miccinilli S, Bravi M, Ranieri F, et al. Literature Review on the Effects of tDCS Coupled with Robotic Therapy in Post Stroke Upper Limb Rehabilitation. Frontiers in human neuroscience. 2017;11:268.
53. Elsner B, Kugler J, Pohl M, Mehrholz J. Transcranial direct current stimulation (tDCS) for improving activities of daily living, and physical and cognitive functioning, in people after stroke. The Cochrane database of systematic reviews. 2016: CD009645.
54. Tedesco Triccas L, Burridge JH, Hughes AM, Pickering RM, Desikan M, Rothwell JC, et al. Multiple sessions of transcranial direct current stimulation and upper extremity rehabilitation in stroke: A review and meta-analysis. Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology. 2016;127:946-55.
55. Valkenborghs SR, van Vliet P, Nilsson M, Zalewska K, Visser MM, Erickson KI, et al. Aerobic exercise and consecutive task-specific training (AExaCTT) for upper limb recovery after stroke: A randomized controlled pilot study. Physiotherapy research international : the journal for researchers and clinicians in physical therapy. 2019:e1775.

56. Firth N, Barker RN, Hayward KS, Bernhardt J, Bellingan M, Gunnarsson R. Safety and efficacy of recovery-promoting drugs for motor function after stroke: A systematic review of randomized controlled trials. J Rehabil Med. 2019;51:319-30.
57. Collaboration FT. Effects of fluoxetine on functional outcomes after acute stroke (FOCUS): a pragmatic, double-blind, randomised, controlled trial. Lancet (London, England). 2019;393:265-74.
58. Ford GA, Bhakta BB, Cozens A, Hartley S, Holloway I, Meads D, et al. Safety and efficacy of co-careldopa as an add-on therapy to occupational and physical therapy in patients after stroke (DARS): a randomised, double-blind, placebo-controlled trial. Lancet Neurol. 2019;18:530-8.
59. Papadopoulos CM, Tsai SY, Guillen V, Ortega J, Kartje GL, Wolf WA. Motor recovery and axonal plasticity with short-term amphetamine after stroke. Stroke. 2009;40(1):294-302.
60. Beltran EJ, Papadopoulos CM, Tsai SY, Kartje GL, Wolf WA. Long-term motor improvement after stroke is enhanced by short-term treatment with the alpha-2 antagonist, atipamezole. Brain Res. 2010;1346:174-82.

Supplemental 3: Supporting reference list for Figure 3 A-E.

A. HOW MUCH:

1. MacLellan CL, Keough MB, Granter-Button S, Chernenko GA, Butt S, Corbett D. A critical threshold of rehabilitation involving brain-derived neurotrophic factor is required for poststroke recovery. Neurorehabil Neural Repair. 2011;25:740-8.
2. Bell JA, Wolke ML, Ortez RC, Jones TA, Kerr AL. Training Intensity Affects Motor Rehabilitation Efficacy Following Unilateral Ischemic Insult of the Sensorimotor Cortex in C57BL/6 Mice. NeuroRehabilitation and Neural Repair. 2015;29:590-598.
3. Jeffers MS, Karthikeyan S, Gomez-Smith M, Gasinzigwa S, Achenbach J, Feiten A, et al. Does Stroke Rehabilitation Really Matter? Part B: An algorithm for prescribing an effective intensity of rehabilitation. Neurorehabil Neural Repair. 2018;32:73-83.
4. Nudo RJ, Wise BM, SiFuentes F, Milliken GW. Neural substrates for the effects of rehabilitative training on motor recovery after ischemic infarct. Science. 1996;272:1791-4.
5. Friel KM, Nudo RJ. Recovery of motor function after focal cortical injury in primates: compensatory movement patterns used during rehabilitative training. Somatosens Mot Res. 1998;15:173-89.
6. Murata YN, Higo N, Oishi T, Yamashita A, Matsuda K, Hayashi M, et al. Effects of motor training on the recovery of manual dexterity after primary motor cortex lesion in macaque monkeys. Journal of neurophysiology. 2008;99:773-86.
7. Barbay S, Plautz EJ, Friel KM, Frost SB, Dancause N, Stowe AM, et al. Behavioral and neurophysiological effects of delayed training following a small ischemic infarct in primary motor cortex of squirrel monkeys. Experimental Brain Research. 2006;169:106-16.
8. Schneider EJ, Lannin NA, Ada L, Schmidt J. Increasing the amount of usual rehabilitation improves activity after stroke: a systematic review. J Physiother. 2016;62:182-7.
9. Lohse KR, Lang CE, Boyd LA. Is more better? Using meta-data to explore dose-response relationships in stroke rehabilitation. Stroke. 2014;45:2053-8.
10. Abdullahi A. Effects of Number of Repetitions and Number of Hours of Shaping Practice during Constraint-Induced Movement Therapy: A Randomized Controlled Trial. Neurology Research International. 2018;5496408.
11. Donaldson C, Tallis R, Miller S, Sunderland A, Lemon R, Pomeroy V. Effects of conventional physical therapy and functional strength training on upper limb motor recovery after stroke: A randomized phase II study. Neurorehabilitation and Neural Repair. 2009;23:389-97.
12. Glasgow Augmented Physiotherapy Study g. Can augmented physiotherapy input enhance recovery of mobility after stroke? A randomized controlled trial. Clin Rehabil. 2004;18:529-37.
13. Burgar CG, Lum PS, Scremin AM, Garber SL, Van der Loos HF, Kenney D, et al. Robot-assisted upper-limb therapy in acute rehabilitation setting following stroke: Department of Veterans Affairs multisite clinical trial. J Rehabil Res Dev. 2011;48:445-58.
14. Kwakkel G, Wagenaar R, Twisk J, Lankhorst G, Koetsier J. Intensity of leg and arm training after primary middle-cerebral-artery stroke:A randomised trial.The Lancet.1999;354:191-6.
15. Han C, Wang Q, Meng PP, Qi MZ. Effects of intensity of arm training on hemiplegic upper extremity motor recovery in stroke patients: a randomized controlled trial. Clin Rehabil. 2013;27:75-81.
16. Kowalczewski J, Gritsenko V, Ashworth N, Ellaway P, Prochazka A. Upper-extremity functional electric stimulation-assisted exercises on a workstation in the subacute phase of stroke recovery. Archives of Physical Medicine and Rehabilitation. 2007;88:833-9.
17. Page SJ, Levin L, Hermann V, Dunning K, Levine P. Longer versus shorter daily durations of electrical stimulation during task-specific practice in moderately impaired stroke. Arch Phys Med Rehabil. 2012;93:200-6.
18. Lang CE, Strube MJ, Bland MD, Waddell KJ, Cherry-Allen KM, Nudo RJ, et al. Dose response of task-specific upper limb training in people at least 6 months poststroke: A phase II, single-blind, randomized, controlled trial. Annals of Neurology. 2016;80:342-54.

B. WHAT

1. Jeffers MS, Corbett D. Does Stroke Rehabilitation Really Matter? Part A: Proportional Stroke Recovery in the Rat. Neurorehabil Neural Repair. 2018;32:3-6.
2. Jeffers MS, Corbett D. Synergistic Effects of Enriched Environment and Task-Specific Reach Training on Poststroke Recovery of Motor Function. Stroke. 2018;49:1496-503.
3. Jeffers MS, Karthikeyan S, Gomez-Smith M, Gasinzigwa S, Achenbach J, Feiten A, et al. Does Stroke Rehabilitation Really Matter? Part B: An algorithm for prescribing an effective intensity of rehabilitation. Neurorehabil Neural Repair. 2018;32:73-83.
4. Friel KM, Heddings AA, Nudo RJ. Effects of postlesion experience on behavioral recovery and neurophysiologic reorganization after cortical injury in primates. Neurorehabil Neural Repair. 2000;14:187-98.
5. Corbetta D, Sirtori V, Castellini G, Moja L, Gatti R. Constraint-induced movement therapy for upper extremities in people with stroke. The Cochrane database of systematic reviews. 2015:CD004433.
6. Etoom M, Hawamdeh M, Hawamdeh Z, Alwardat M, Giordani L, Bacciu S, et al. Constraint-induced movement therapy as a rehabilitation intervention for upper extremity in stroke patients: systematic review and meta-analysis. International journal of rehabilitation research Internationale Zeitschrift fur Rehabilitationsforschung Revue internationale de recherches de readaptation. 2016;39:197-210.
7. Castellini G, Gianola S, Banzi R, Corbetta D, Gatti R, Sirtori V, et al. Constraint-induced movement therapy: trial sequential analysis applied to Cochrane collaboration systematic review results. Trials. 2014;15:512.
8. Kwakkel G, Veerbeek JM, van Wegen EE, Wolf SL. Constraint-induced movement therapy after stroke. Lancet Neurol. 2015;14:224-34.
9. French B, Thomas LH, Coupe J, McMahon NE, Connell L, Harrison J, et al. Repetitive task training for improving functional ability after stroke. The Cochrane database of systematic reviews. 2016;11:CD006073.
10. Veerbeek JM, Langbroek-Amersfoort AC, van Wegen EE, Meskers CG, Kwakkel G. Effects of Robot-Assisted Therapy for the Upper Limb After Stroke. Neurorehabil Neural Repair. 2017;31:107-21.
11. Mehrholz J, Hadrich A, Platz T, Kugler J, Pohl M. Electromechanical and robot-assisted arm training for improving generic activities of daily living, arm function and arm muscle strength after stroke. Cochrane Database of Systematic Reviews. 2012;6:CD006876.
12. McCabe J, Monkiewicz M, Holcomb J, Pundik S, Daly JJ. Comparison of robotics, functional electrical stimulation, and motor learning methods for treatment of persistent upper extremity dysfunction after stroke: a randomized controlled trial. Arch Phys Med Rehabil. 2015;96:981-90.
13. Daly JJ, McCabe JP, Holcomb J, Monkiewicz M, Gansen J, Pundik S. Long-Dose Intensive Therapy Is Necessary for Strong, Clinically Significant, Upper Limb Functional Gains and Retained Gains in Severe/Moderate Chronic Stroke. Neurorehabil Neural Repair. 2019:1545968319846120.
14. Winstein CJ, Wolf SL, Dromerick AW, Lane CJ, Nelsen MA, Lewthwaite R, et al. Effect of a Task-Oriented Rehabilitation Program on Upper Extremity Recovery Following Motor Stroke: The ICARE Randomized Clinical Trial. JAMA. 2016;315:571-81.
15. Hunter SM, Johansen-Berg H, Ward N, Kennedy NC, Chandler E, Weir CJ, et al. Functional Strength Training and Movement Performance Therapy for Upper Limb Recovery Early Poststroke-Efficacy, Neural Correlates, Predictive Markers, and Cost-Effectiveness: FAST-INdiCATE Trial. Front Neurol. 2017;8:733.
16. Hoffmann TC, Glasziou PP, Boutron I, Milne R, Perera R, Moher D, et al. Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. BMJ. 2014;348:1687.
17. Kwakkel G, Van Wegen EEH, Burridge JH, Winstein C, Alt Murphy M, Levin MF, Krakauer JW. Standardized measurement of quality of upper limb movement after stroke:

Consensus-based core recommendations from the Second Stroke Recovery and Rehabilitation Roundtable. International Journal of Stroke. Accepted 13 June 2019.

C. WHEN

1. Biernaskie J, Chernenko G, Corbett D. Efficacy of rehabilitative experience declines with time after focal ischemic brain injury. Journal of Neuroscience. 2004;24:1245-54.
2. Biernaskie J, Corbett D. Enriched rehabilitative training promotes improved forelimb motor function and enhanced dendritic growth after focal ischemic injury. J Neurosci. 2001;21:5272-80.
3. Nudo RJ, Wise BM, SiFuentes F, Milliken GW. Neural substrates for the effects of rehabilitative training on motor recovery after ischemic infarct. Science. 1996;272:1791-4.
4. Wahl AS, Omlor W, Rubio JC, Chen JL, Zheng H, Schroter A, et al. Neuronal repair. Asynchronous therapy restores motor control by rewiring of the rat corticospinal tract after stroke. Science. 2014;344:1250-5.
5. Jeffers MS, Corbett D. Synergistic Effects of Enriched Environment and Task-Specific Reach Training on Poststroke Recovery of Motor Function. Stroke. 2018;49:1496-503.
6. Jeffers MS, Hoyles A, Morshead C, Corbett D. Epidermal growth factor and erythropoietin infusion accelerate functional recovery in combination with rehabilitation. Stroke. 2014;45:1856-8.
7. Clarke J, Mala H, Windle V, Chernenko G, Corbett D. The effects of repeated rehabilitation "tune-ups" on functional recovery after focal ischemia in rats. Neurorehabil Neural Repair. 2009;23:886-94.
8. Hubbard IJ, Parsons MW, Neilson C, Carey LM. Task-specific training: evidence for and translation into clinical practice. Occupational Therapy International. 2009;16:175-89.
9. Kwakkel G, Winters C, van Wegen EE, Nijland RH, van Kuijk AA, Visser-Meily A, et al. Effects of Unilateral Upper Limb Training in Two Distinct Prognostic Groups Early After Stroke: The EXPLICIT-Stroke Randomized Clinical Trial. Neurorehabil Neural Repair. 2016;30:804-16.
10. Yu C, Wang W, Zhang Y, Wang Y, Hou W, Liu S, et al. The Effects of Modified Constraint-Induced Movement Therapy in Acute Subcortical Cerebral Infarction. Frontiers in human neuroscience. 2017;11:265.
11. Dromerick AW, Lang CE, Birkenmeier RL, Wagner JM, Miller JP, Videen TO, et al. Very Early Constraint-Induced Movement during Stroke Rehabilitation (VECTORS). A single-center RCT. Neurology. 2009;73:195-201.
12. Winstein CJ, Wolf SL, Dromerick AW, Lane CJ, Nelsen MA, Lewthwaite R, et al. Effect of a Task-Oriented Rehabilitation Program on Upper Extremity Recovery Following Motor Stroke: The ICARE Randomized Clinical Trial. JAMA. 2016;315:571-81.
13. Han C, Wang Q, Meng PP, Qi MZ. Effects of intensity of arm training on hemiplegic upper extremity motor recovery in stroke patients: a randomized controlled trial. Clin Rehabil. 2013;27:75-81.
14. Wolf SL, Winstein CJ, Miller JP, Taub E, Uswatte G, Morris D, et al. Effect of constraint-induced movement therapy on upper extremity function 3 to 9 months after stroke: the EXCITE randomized clinical trial. JAMA. 2006;296:2095-104.
15. Dromerick AW, Edwardson MA, Edwards DF, Giannetti ML, Barth J, Brady KP, et al. Critical periods after stroke study: translating animal stroke recovery experiments into a clinical trial. Frontiers in human neuroscience. 2015;9:231.
16. Langhorne P, Collier JM, Bate PJ, Thuy MN, Bernhardt J. Very early versus delayed mobilisation after stroke. The Cochrane database of systematic reviews. 2018;10:CD006187.

D. WHO

1. Jeffers MS, Karthikeyan S, Gomez-Smith M, Gasinzigwa S, Achenbach J, Feiten A, et al. Does Stroke Rehabilitation Really Matter? Part B: An algorithm for prescribing an effective intensity of rehabilitation. Neurorehabil Neural Repair. 2018;32:73-83.
2. Karthikeyan S, Jeffers MS, Carter A, Corbett D. Characterizing Spontaneous Motor Recovery Following Cortical and Subcortical Stroke in the Rat. Neurorehabil Neural Repair. 2019;33:27-37.
3. Darling WG, Pizzimenti MA, Rotella DL, Hynes SM, Ge J, Stilwell-Morecraft K, et al. Sensorimotor cortex injury effects on recovery of contralesional dexterous movements in Macaca mulatta. Exp Neurol. 2016;281:37-52.
4. Darling WG, Pizzimenti MA, Rotella DL, Peterson CR, Hynes SM, Ge J, et al. Volumetric effects of motor cortex injury on recovery of dexterous movements. Exp Neurol. 2009;220:90-108.
5. Hayward KS, Schmidt J, Lohse KR, Peters S, Bernhardt J, Lannin NA, et al. Are we armed with the right data? Pooled individual data review of biomarkers in people with severe upper limb impairment after stroke. NeuroImage Clinical. 2017;13:310-9.
6. Kim B, Winstein C. Can Neurological Biomarkers of Brain Impairment Be Used to Predict Poststroke Motor Recovery? A Systematic Review. Neurorehabil Neural Repair. 2017;31:3-24.
7. Winters C, Heymans MW, van Wegen EE, Kwakkel G. How to design clinical rehabilitation trials for the upper paretic limb early post stroke? Trials. 2016;17:468.
8. Simpson L, Hayward KS, McPeake M, Eng JJ. An updated distribution of upper limb weakness post stroke: are fewer people experiencing arm weakness today? International Journal of Stroke. 2018;13:41.
9. Stinear CM, Barber PA, Petoe M, Anwar S, Byblow WD. The PREP algorithm predicts potential for upper limb recovery after stroke. Brain. 2012;135:2527-35.
10. Stinear CM, Byblow WD, Ackerley SJ, Smith MC, Borges VM, Barber PA. PREP2: A biomarker-based algorithm for predicting upper limb function after stroke. Ann Clin Transl Neurol. 2017;4:811-20.
11. Beebe JA, Lang CE. Active range of motion predicts upper extremity function 3 months after stroke. Stroke. 2009;40:1772-9.
12. Levy RM, Harvey RL, Kissela BM, Winstein CJ, Lutsep HL, Parrish TB, et al. Epidural Electrical Stimulation for Stroke Rehabilitation: Results of the Prospective, Multicenter, Randomized, Single-Blinded Everest Trial. Neurorehabilitation and Neural Repair. 2016;30:107-19.
13. Riley JD, Le V, Der-Yeghiaian L, See J, Newton JM, Ward NS, et al. Anatomy of stroke injury predicts gains from therapy. Stroke. 2011;42:421-6.
14. Cassidy JM, Tran G, Quinlan EB, Cramer SC. Neuroimaging Identifies Patients Most Likely to Respond to a Restorative Stroke Therapy. Stroke. 2018;49:433-8.

E. ADJUVANT

1. Papadopoulos CM, Tsai SY, Guillen V, Ortega J, Kartje GL, Wolf WA. Motor recovery and axonal plasticity with short-term amphetamine after stroke. Stroke. 2009;40:294-302.
2. Feeney DM, Gonzalez A, Law WA. Amphetamine, haloperidol, and experience interact to affect rate of recovery after motor cortex injury. Science. 1982;217:855-7.
3. Adkins-Muir DL, Jones TA. Cortical electrical stimulation combined with rehabilitative training: enhanced functional recovery and dendritic plasticity following focal cortical ischemia in rats. Neurol Res. 2003;25:780-8.
4. Adkins DL, Campos P, Quach D, Borromeo M, Schallert K, Jones TA. Epidural cortical stimulation enhances motor function after sensorimotor cortical infarcts in rats. Exp Neurol. 2006;200:356-70.
5. Adkins DL, Hsu JE, Jones TA. Motor cortical stimulation promotes synaptic plasticity and behavioral improvements following sensorimotor cortex lesions. Exp Neurol. 2008;212:14-28.
6. Boychuk JA, Adkins DL, Kleim JA. Distributed versus focal cortical stimulation to enhance motor function and motor map plasticity in a rodent model of ischemia. Neurorehabil Neural Repair. 2011;25:88-97.
7. Boychuk JA, Schwerin SC, Thomas N, Roger A, Silvera G, Liverpool M, et al. Enhanced Motor Recovery After Stroke With Combined Cortical Stimulation and Rehabilitative Training Is Dependent on Infarct Location. Neurorehabil Neural Repair. 2016;30:173-81.
8. Plautz EJ, Barbay S, Frost SB, Zoubina EV, Stowe AM, Dancause N, et al. Effects of Subdural Monopolar Cortical Stimulation Paired With Rehabilitative Training on Behavioral and Neurophysiological Recovery After Cortical Ischemic Stroke in Adult Squirrel Monkeys. Neurorehabil Neural Repair. 2016;30:159-72.
9. Ng KL, Gibson EM, Hubbard R, Yang J, Caffo B, O'Brien RJ, et al. Fluoxetine Maintains a State of Heightened Responsiveness to Motor Training Early After Stroke in a Mouse Model. Stroke. 2015;46:2951-60.
10. Barbay S, Plautz EJ, Zoubina E, Frost SB, Cramer SC, Nudo RJ. Effects of postinfarct myelin-associated glycoprotein antibody treatment on motor recovery and motor map plasticity in squirrel monkeys. Stroke. 2015;46:1620-5.
11. Jeffers MS, Hoyles A, Morshead C, Corbett D. Epidermal growth factor and erythropoietin infusion accelerate functional recovery in combination with rehabilitation. Stroke. 2014;45:1856-8.
12. Wahl AS, Omlor W, Rubio JC, Chen JL, Zheng H, Schroter A, et al. Neuronal repair. Asynchronous therapy restores motor control by rewiring of the rat corticospinal tract after stroke. Science. 2014;344:1250-5.
13. Barbay S, Zoubina EV, Dancause N, Frost SB, Eisner-Janowicz I, Stowe AM, et al. A single injection of D-amphetamine facilitates improvements in motor training following a focal cortical infarct in squirrel monkeys. Neurorehabil Neural Repair. 2006;20(4):455-8.
14. Firth N, Barker RN, Hayward KS, Bernhardt J, Bellingan M, Gunnarsson R. Safety and efficacy of recovery-promoting drugs for motor function after stroke: A systematic review of randomized controlled trials. J Rehabil Med. 2019;51:319-30.
15. Collaboration FT. Effects of fluoxetine on functional outcomes after acute stroke (FOCUS): a pragmatic, double-blind, randomised, controlled trial. The Lancet. 2019;393:265-74.
16. Chollet F, Tardy J, Albucher JF, Thalamas C, Berard E, Lamy C, et al. Fluoxetine for motor recovery after acute ischaemic stroke (FLAME): a randomised placebo-controlled trial. Lancet Neurol. 2011;10:123-30.
17. Ford GA, Bhakta BB, Cozens A, Hartley S, Holloway I, Meads D, et al. Safety and efficacy of co-careldopa as an add-on therapy to occupational and physical therapy in patients after stroke (DARS): a randomised, double-blind, placebo-controlled trial. Lancet Neurol. 2019;18:530-8.
18. Graham C, Lewis S, Forbes J, Mead G, Hackett ML, Hankey GJ, et al. The FOCUS, AFFINITY and EFFECTS trials studying the effect(s) of fluoxetine in patients with a recent stroke: statistical and health economic analysis plan for the trials and for the individual patient data meta-analysis. Trials. 2017;18:627.

19. Elsner B, Kugler J, Pohl M, Mehrholz J. Transcranial direct current stimulation (tDCS) for improving activities of daily living, and physical and cognitive functioning, in people after stroke. The Cochrane database of systematic reviews. 2016: CD009645.
20. Tedesco Triccas L, Burridge JH, Hughes AM, Pickering RM, Desikan M, Rothwell JC, et al. Multiple sessions of transcranial direct current stimulation and upper extremity rehabilitation in stroke: A review and meta-analysis. Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology. 2016;127:946-55.
21. Simonetti D, Zollo L, Milighetti S, Miccinilli S, Bravi M, Ranieri F, et al. Literature Review on the Effects of tDCS Coupled with Robotic Therapy in Post Stroke Upper Limb Rehabilitation. Frontiers in human neuroscience. 2017;11:268.