HTA Austria
Austrian Institute for
Health Technology Assessment
GmbH

Robotics and functional electrical stimulation for stroke rehabilitation

Systematic Review

Final report

AIHTA Project Report No.: 128 | ISSN: 1993-0488 | ISSN-online: 1993-0496

HTA Austria
Austrian Institute for
Health Technology Assessment
GmbH

Robotics and functional electrical stimulation for stroke rehabilitation

Systematic Review

Vienna, April 2021

Project Team

Project leader: Gregor Goetz, MSSc MPH

Authors: Gregor Goetz, MSSc MPH
Melanie Walter, PhD Eu-MSc BSc
Kathrin Wohlhöfner, B.A.
Heike Wittenberg, MSc, St. Mauritius Therapieklinik, Meerbusch
Dr.in Susanne Saal, Institut für Gesundheits- und Pflegewissenschaft, Martin-Luther-Universität Halle-Wittenberg
Dr. med. Klaus Martin Stephan, SRH Gesundheitszentrum Waldbronn, Waldbronn
Priv.-Doz. Dr. med. Christian Dohle, MEDIAN Klinik Berlin-Kladow und Centrum für Schlaganfallforschung, Charité – Universitätsmedizin Berlin

Project Support

Systematic literature search: Tarquin Mittermayr, BA (Hons) MA

External Review: Dr. med. Klemens Fheodoroff, Abteilung für Neurorehabilitation, Gailtal-Klinik Hermagor

Internal Review: Priv.-Doz.in Dr.in phil. Claudia Wild

Correspondence: gregor.goetz@aihta.at

Cover photo: © natiavektor – stock.adobe.com

The study was conducted in collaboration with the working group of the Deutsche Gesellschaft für Neurorehabilitation (DGNR), member of the Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF).

This report should be referenced as follows:

Goetz G, Walter M, Wohlhöfner K, Wittenberg H, Saal S, Stephan K M, Dohle C. Robotics and functional electrical stimulation for stroke rehabilitation: a systematic review of effectiveness and safety. AIHTA Project report No.128; 2020. Vienna: HTA Austria – Austrian Institute for Health Technology Assessment GmbH.

Conflict of interest

All authors and the reviewers involved in the production of this report have declared they have no conflicts of interest in relation to the technology assessed according to the Uniform Requirements of Manuscripts Statement of Medical Journal Editors (www.imce.org).

Disclaimer

The external reviewers did not co-author the scientific report and do not necessarily all agree with its content. Only the HTA Austria – AIHTA GmbH is responsible for errors or omissions that could persist. The final version and the policy recommendations are under the full responsibility of the HTA Austria – AIHTA GmbH.

CONTENT INFORMATION

Publisher:
HTA Austria – Austrian Institute for Health Technology Assessment GmbH
Garnisongasse 7/Top 20 | 1090 Vienna – Austria
https://www.aihta.at/

Responsible for content:
Priv.-Doz. Dr. phil. Claudia Wild, managing director

AIHTA Project Reports do not appear on a regular basis and serve to publicize the research results of the Austrian Institute for Health Technology Assessment.

AIHTA Project Reports are only available to the public via the Internet at http://eprints.aihta.at/view/types/hta_report.html.

AIHTA Project Report No.: 128

ISSN 1993-0488

ISSN online 1993-0496

© 2021 AIHTA – All rights reserved

Content

List of figures

List of tables

List of abbreviations

6MWT .....6-Minutes Walk Test
AAR.....Arm Activity Ratio
ADL .....Activities of Daily Living
AE.....Adverse Events
AFO.....Ankle Foot Orthosis
AGREE .....Appraisal of Guidelines, Research and Evaluation
AHA .....American Heart Association
AIHTA .....Austrian Institute for Health Technology Assessment
AL.....Activity limitations
ARAT .....Action Research Arm Test
AtW .....Ability to Walk
AWMF .....Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften
BAL .....Balance
BBS.....Berg Balance Scale
BBT .....Box and Block Test
BF .....Body Function and Structure
BI .....Barthel Index
BWS .....Body Weight Support
CAHAI .....Chedoke Arm and Hand Activity Inventory
CE.....Conformité Européenne
CEBM .....Oxford Centre for Evidence Based Medicine
CMSA.....Chedoke McMaster Disability Inventory
COVS .....Clinical Outcomes Variable Scale
DALY.....Disability Adjusted Life Years
DGNKN.....Federal Association for Rehabilitation e. V. and the German Society for Neurorehabilitation e. V.
DoF .....Degrees of Freedom
EMG.....Electromyography
FAC.....Functional Ambulatory Category
FAT.....Frenchay Arm Test
FDA .....Food and Drug Administration
FES.....Functional Electrical Stimulation
FIM .....Functional Independence Measure
FMA.....Fugl-Meyer Assessment of Motor Recovery after Stroke
GBD .....Global Burden of Diseases
GD.....Gait distance
GRADE.....Grading of Recommendations, Assessment, Development and Evaluation
HAL .....Hybrid Assistive Limb

HRQoL .....Health-related Quality of Life
JHD .....Jamar Hand Dynamometer
JTHFT .....Jebsen-Taylor Hand Function Test
LDL.....Low Density Lipoprotein
LoE.....Level of Evidence
MAL .....Motor Activity Log
MAS .....Modified Ashworth Scale
MI.....Motricity Index
MP.....Motor Power Score
MRC.....Medical Research Council
MS .....Muscle Strength
MSS .....Motor Status Scale
NMES .....Neuromuscular Electrical Stimulation
NSA.....Nottingham Sensory Assessment
PAS.....Patient Satisfaction
PEDro .....Physiotherapy Evidence Database
PICO .....Population, Intervention, Control and Outcomes
POMA .....Performance Oriented Mobility Assessment
PRISMA.....Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA.....Patient satisfaction
QoL .....Quality of Life
RAR.....Robot Assisted Rehabilitation
RAGT.....Robot Assisted Gait Training
RCT.....Randomised Controlled Trial
RELHFT .....Rehabilitation Engineering Laboratory Hand Function Test
ReMoS.....Rehabilitation der Mobilität nach Schlagafall
RFTHUE.....Rancho Functional Test for the Hemiplegic/Paretic Upper Extremity
RMI.....Rivermead Mobility Index
ROM.....Active range of motion
SAE .....Serious Adverse Events
SF-36.....Short Form-36
SIAS .....Stroke Impairment Assessment Set
SIS .....Stroke Impact Scale
SIS-ADL .....Stroke Impact Scale
TCT.....Trunk Control Test
TUG .....Timed Up and Go Test
UEFT .....Upper Extremity Function Test
WHO-ICTRP .....World Health Organisation-International Clinical Trials Registry Platform
WMFT .....Wolf Motor Function Test
WS.....Walking Speed

Executive Summary

Introduction

post-stroke patients suffer from functional deficits

Post-stroke patients often suffer from a hemiparesis affecting the functional abilities of lower and/or upper extremities. Improving walking and everyday activities are therefore important rehabilitation goals for these patients.

robotic assisted rehabilitation and functional electrical stimulation as supplementary measures in stroke rehabilitation

Robotic assisted rehabilitation (RAR) and functional electrostimulation (FES) can, among others, be used as a supplement to conventional rehabilitation in post-stroke patients. The use of RAR could have the advantage of allowing more intensive and frequent therapy (by increasing the motivation to train), which at the same time reduces the effort of the physiotherapist. FES is a targeted application of electrical stimulation inducing muscle contractions supporting motor activities. The electrical stimulation takes place during a functional movement and may, inter alia, strengthen the muscle and improve blood circulation or blood flow.

additional clinical benefit?

Yet, the additional clinical benefit of using RAR and FES in the rehabilitation of post-stoke patients with a hemiparesis is unclear. Hence, the purpose of this report was to evaluate whether there is a clinical benefit of using RAR or FES in stroke rehabilitation when compared to standard rehabilitation alone.

Methods

systematic review of effectiveness and safety lower limb: Update of evidence of AWMF guideline

For lower limb stroke rehabilitation, we conducted two systematic reviews to evaluate the potential clinical benefit of RAR and FES with regard to functional outcomes such as ability to walk and activities of daily living. A systematic literature search was hereby carried out in five databases. Two researchers conducted the study selection, data extraction and assessment of methodological quality of the studies. GRADE (Grading of Recommendations, Assessment, Development and Evaluation) was used to synthesize the evidence. The evidence synthesis was created on the basis of three sub-interventions for RAR and seven sub-interventions for FES. We only included studies with an acceptable quality rating – judged with a level of evidence of 1b according to the evidence hierarchy.

upper limb: summary of evidence synthesis

For upper limb stroke rehabilitation, we have summarized the evidence identified by a recent high quality AWMF S3 guideline, applying our initial eligibility criteria for RCTs.

Results

lower limb: RAR: 11 RCTs esp. in favour of end-effectors; FES: 17 RCTs, insufficient evidence to show superiority

For lower limb rehabilitation, the evidence consisted of eleven RCTs for RAR and further 17 RCTs for FES. The evidence supports some types of RAR (especially end-effector based gait training) for stroke rehabilitation for patients in the subacute stadium, dependant on their clinical deficit. Insufficient evidence was found to prove that any of the FES interventions combined with standard rehabilitation was superior to standard rehabilitation alone, although the evidence suggests that some sub-interventions of FES (tilt sensor FES systems) are non-inferior when compared to ankle-foot-orthoses in patients with drop foot.

upper limb: AWMF S3 guideline found evidence supporting RAR but insufficient evidence for FES

For upper limb stroke rehabilitation, the AWMF S3 guideline found evidence consisting of one Cochrane SR and 16 RCTs for RAR and nine RCTs for FES that fulfilled our inclusion criteria. The evidence identified by the guideline supports arm robot therapies including both exoskeletons and other electromechanical active robotic devices especially for patients in the subacute stadium. For FES, the AWMF S3 guideline found *low* quality evidence demonstrating that FES, indicated for patients with severe incomplete hand paresis and partially preserved proximal motoric function (movement and holding function), can be used for inducing grasping and releasing or finger and hand extension combined with training of everyday activities.

Conclusion

evidence indicates that RAR may yield a clinical benefit; evidence is insufficient for FES

The identified evidence indicates that RAR may yield a clinical benefit in stroke rehabilitation in the subacute stadium, dependant on their clinical deficit.

The evidence is insufficient to show superiority or inferiority of FES and standard rehabilitation in comparison to standard rehabilitation alone (although some devices were proven non-inferior).

health economic evaluations essential

In light of numerous therapeutic options available in stroke rehabilitation, often with limited proven benefit, but increased costs, health economic evaluations for these interventions that showed a certain clinical benefit or at least non-inferiority is recommended. Here, the focus should be on relieving the physiotherapist's workload (both in terms of time and physical). For such an evaluation, it is essential to consider the general conditions or the organizational setting and the severity of the stroke. On the other hand, a disinvestment in treatment modalities that are not proven by evidence or are not cost-effective should be considered.

Zusammenfassung

Hintergrund

starke Einschränkungen der Körperfunktionen nach Schlaganfall

Nach Schlaganfällen leiden Betroffene häufig unter (unvollständigen) zentralen Lähmungen (Hemiparesen). Diese Hemiparesen können sowohl die unteren als auch die oberen Extremitäten betreffen und schränken die Körperfunktionalität stark ein. Die Verbesserung des Gehens und der Alltagsaktivitäten stellen daher wesentliche Rehabilitationsziele für Patient*innen mit Insult-bedingten Hemiparesen in der subakuten und chronischen Phase des Schlaganfalls dar.

roboterassistierte Rehabilitation und funktionelle Elektrostimulation als Zusatz bzw. Unterstützung der Standardrehabilitation

Roboterassistierte Rehabilitation (RAR) und funktionelle Elektrostimulation (FES) können vor allem ergänzend zur herkömmlichen Rehabilitation eingesetzt werden. Man verspricht sich, dass diese Verfahren die Rehabilitation von Schlaganfallpatient*innen begünstigen: Bei der Verwendung von RAR könnten Vorteile darin liegen, dass eine intensivere und häufigere (durch Steigerung der Trainingsmotivation) Therapie ermöglicht wird, die gleichzeitig den Aufwand des/der Physiotherapeut*in reduziert. Bei der FES handelt es sich um eine gezielte Anwendung von elektrischer Stimulation, welche Muskelkontraktionen induziert und dabei motorische Aktivitäten im Allgemeinen unterstützt. Die elektrische Stimulation erfolgt während eines funktionellen Bewegungskontextes: Man verspricht sich dadurch, unter anderem, eine Stärkung des Muskels und eine verbesserte Durchblutung bzw. einen verbesserten Blutfluss.

Ziel: Evaluierung des klinischen Nutzens und der Sicherheit

Der klinische Zusatznutzen von RAR und der FES bei Insult-bedingten Hemiparesen ist jedoch unklar. Daher gilt es zu klären, ob wissenschaftliche Nachweise für einen zusätzlichen Nutzen von RAR oder FES als Ergänzung zu herkömmlichen Rehabilitationsinterventionen vorliegen.

Forschungsfragen: Ist eine zusätzliche Rehabilitation mit Robotern oder funktioneller Elektrostimulation der herkömmlichen Rehabilitation überlegen?

Das Ziel dieses Berichts war es, den klinischen Zusatznutzen von RAR und FES innerhalb der Schlaganfallrehabilitation zu evaluieren. Folgende Forschungsfragen sollten beantwortet werden:

- Ist **RAR** als Zusatz zur herkömmlichen Rehabilitation bei Patient*innen mit Insult-bedingten zentralen Lähmungen der **unteren Extremitäten** im Vergleich zur Standardrehabilitation im stationären oder ambulanten Setting hinsichtlich der Verbesserung der selbstständigen Gehfähigkeit effektiver und hinsichtlich unerwünschter Ereignisse gleich sicher?
- Ist **RAR** als Zusatz zur herkömmlichen Rehabilitation bei Patient*innen mit Insult-bedingten zentralen Lähmungen der **oberen Extremitäten** im Vergleich zur Standardrehabilitation im stationären oder ambulanten Setting hinsichtlich der Verbesserung der Aktivitäten des Alltags effektiver und hinsichtlich unerwünschter Ereignisse gleich sicher?
- Ist die **FES** als Zusatz zur herkömmlichen Rehabilitation bei Patient*innen mit Insult-bedingten zentralen Lähmungen der **unteren Extremitäten** im Vergleich zur Standardrehabilitation im stationären oder ambulanten Setting hinsichtlich der Verbesserung der selbstständigen Gehfähigkeit effektiver und hinsichtlich unerwünschter Ereignisse gleich sicher?

- Ist die **FES** als Zusatz zur herkömmlichen Rehabilitation bei Patient*innen mit Insult-bedingten zentralen Lähmungen der **oberen Extremitäten** im Vergleich zur Standardrehabilitation im stationären oder ambulanten Setting hinsichtlich der Verbesserung der Aktivitäten des Alltags effektiver und hinsichtlich unerwünschter Ereignisse gleich sicher?

Methoden

Methoden: SR der 2 Interventionen bei unteren Extremitäten;

Zusammenfassung der Evidenzsynthese einer AWMF S3 LL für obere Extremitäten

Zur Evaluierung des zusätzlichen klinischen Nutzens bei zumindest vergleichbarer Sicherheit von RAR und FES bei Anwendung an den unteren Extremitäten wurde eine Kooperation mit der ReMoS-AG (Rehabilitation der Mobilität nach Schlaganfall-Arbeitsgruppe) eingegangen, die ihre Leitlinie (AWMF S2) zeitgleich aktualisierte (RAR: ReMoS AG; FES: AIHTA). Es wurden dazu zwei systematische Update-Übersichtsarbeiten erstellt: Die systematische Literatursuche erfolgte in mehreren medizinischen Datenbanken und alle Arbeitsschritte (Studienselektion, Datenextraktion, Qualitätsbeurteilung der eingeschlossenen Studien, GRADE) wurden von 2 Personen durchgeführt. Die Evaluierung des zusätzlichen Nutzens der Technologien bei Anwendung an den oberen Extremitäten basierte gänzlich auf einer rezenten AWMF S3 Leitlinie, welche 2020 publiziert wurde.

entscheidende Endpunkte: Gehfähigkeit und dergleichen sowie „Aktivitäten des Alltags“

Sicherheit: SUE/UE

Als relevante Endpunkte für die Bewertung des klinischen Nutzens von RAR und FES zur Unterstützung der Rehabilitation der unteren Extremitäten wurden Gehfähigkeit, Gehgeschwindigkeit, Gehstrecke und Balance gewählt. Für die Bewertung des klinischen Nutzens der Technologien zur Unterstützung bei der Rehabilitation der oberen Extremitäten wurde der Endpunkt „Aktivitäten des Alltags“ als entscheidend definiert. Zur Bewertung der Sicherheit wurden schwere unerwünschte Ereignisse (SUE) und unerwünschte Ereignisse (UE) als entscheidend definiert.

Ergebnisse

Es konnte eine Vielzahl an Herstellern bzw. Geräten mit unterschiedlichen technischen Charakteristika für die zu evaluierenden Interventionen identifiziert werden:

verfügbare Geräte: RAR (n=32) FES (n=11)

Für die RAR wurden 32 verfügbare Medizinprodukte identifiziert: Davon können 15 Geräte als Unterstützung des Gangtrainings eingesetzt werden und weitere 17 Geräte fokussieren auf die Unterstützung der Armrehabilitation. Es wurden weitere elf FES-Medizinprodukte identifiziert, wovon vier bzw. sieben FES-Geräte als Unterstützung des Gangtrainings bzw. der Armrehabilitation eingesetzt werden können.

Klinischer Nutzen der roboterassistierten Rehabilitation und der funktionellen Elektrostimulation in der Schlaganfallrehabilitation der **unteren Extremitäten**

untere Extremitäten: AWMF LL: 11 RCTs

Für die RAR bei unteren Extremitäten konnten insgesamt elf RCTs mit ausreichender Qualität identifiziert werden. Die Studien untersuchten den Einsatz von stationären Exoskeletten (4 RCTs; subakut und chronisch; n=211), mobilen Exoskeletten (2 RCTs; subakut und chronisch; n=48) und stationären End-Effektoren (5 RCTs; subakut und chronisch; n=361). Hinsichtlich der Anwendung der zu evaluierenden Interventionen bei der Rehabilitation der unteren Extremitäten fand die AWMF S2 Leitlinie:

Stationäre End-Effektoren:

- Moderate Qualität der Evidenz, dass ein Endeffektor gestütztes Training kombiniert mit konventionellem Gehtraining die Gehfähigkeit bei nicht selbstständig gehfähigen Schlaganfallpatient*innen im subakuten Stadium einem rein konventionellen Gehtraining überlegen ist.
- Niedrige bis sehr niedrige Qualität der Evidenz, dass bei Schlaganfallpatient*innen im subakuten Stadium ein Endeffektor gestütztes Gehtraining kombiniert mit konventionellem Gehtraining (in Bezug auf die Endpunkte Gehgeschwindigkeit, Gehstrecke oder Balance) einem rein konventionellen Gehtraining überlegen ist.
- Niedrige Qualität der Evidenz, dass ein Endeffektor gestütztes Gehtraining bei Patient*innen im chronischen Stadium einem konventionellen Gehtraining nicht überlegen ist, um die Gehfähigkeit, Gehgeschwindigkeit, Gehstrecke oder die Balance zu verbessern.

stationäre End-Effektoren: moderate Qualität der Evidenz für Zusatznutzen hinsichtlich der Gehfähigkeit in subakutem Stadium bei nicht gefähigen Patient*innen

Stationäre Exoskelette:

- Moderate Qualität der Evidenz, dass stationäre Exoskelette kombiniert mit konventionellem Gehtraining die Gehfähigkeit und die Balance nicht zusätzlich verbessern.
- Niedrige Qualität der Evidenz, dass stationäre Exoskelette kombiniert mit konventionellem Gehtraining die Gehgeschwindigkeit und die Gehstrecke nicht zusätzlich verbessern.

stationäre Exoskelette: moderate Qualität der Evidenz entgegen Zusatznutzen

Mobile Exoskelette

- Niedrige Qualität der Evidenz, dass mobile Exoskelette kombiniert mit konventionellem Gehtraining keine zusätzliche Verbesserung hinsichtlich der Endpunkte Gehfähigkeit, Gehgeschwindigkeit, Gehstrecke und Balance erzielen.

mobile Exoskelette: niedrige Qualität der Evidenz entgegen Zusatznutzen

Für die FES bei unteren Extremitäten konnten insgesamt 17 RCTs mit ausreichender Qualität zu sieben Subinterventionen/FES Modalitäten identifiziert werden:

FES: 17 RCTs mit 1b LoE

- *FES mit Oberflächenelektroden beim Gehen*
  Die Evidenz, bestehend aus sieben RCTs, war unzureichend, um eine Überlegenheit einer Rehabilitation mit Mehrkanal-FES (2 RCTs; subakut und chronisch; n=53 Patient*innen), Gangtraining mit Flexorreflexstimulation (1 RCT; n=30) und Neigungssensor FES (2 RCTs; chronisch; n=692) im Vergleich zur Standardrehabilitation nachweisen zu können. Moderate Qualität der Evidenz legt nahe, dass eine Rehabilitation mit Nervus peroneus FES (2 RCTs; chronisch; n=142) einer Standardrehabilitation nicht überlegen ist.

  FES mit Oberflächenelektroden: unzureichende Evidenz für Zusatznutzen

  Es konnte eine Nicht-Unterlegenheit der Neigungssensor-FES (2 RCTs; chronisch; n=692) im Vergleich zur Standardrehabilitation mit Fußgelenksorthesen festgestellt werden. Die Qualität der Evidenz wurde hierbei als moderat eingestuft. Schwerwiegende Nebenwirkungen wurden für diese Nicht-Unterlegenheitsanalyse ebenfalls berücksichtigt.

  Nicht-Unterlegenheit im Vergleich zu Fußgelenksorthesen

- *Elektrostimulation des Peroneus-Nervs mit implantiertem System beim Gehen*
  Die Evidenz, bestehend aus einem RCT (chronisch; n=25), ist unzureichend, um eine Überlegenheit einer Rehabilitation mit einer Elektrostimulation des Peroneus-Nervs (implantiert) während des Gehens im Vergleich zur Standardrehabilitation nachweisen zu können. Die Qualität der Evidenz wurde als niedrig eingestuft.

  Elektrostimulation des Peroneus-Nervs: unzureichende Evidenz

Mehrkanal FES mit perk. Drahtelektroden: unzureichende Evidenz

- *Mehrkanal-FES mit perkutanen Drahtelektroden*
  Die Evidenz, bestehend aus einem RCT (chronisch; n=31), ist unzureichend, um eine Überlegenheit einer Rehabilitation mit Mehrkanal-FES mit perkutanen Drahtelektroden im Vergleich zur Standardrehabilitation nachweisen zu können. Die Qualität der Evidenz wurde als niedrig eingestuft.

FES in Kombination mit elektromech. Gangtrainer: unzureichende Evidenz

- *FES in Kombination mit elektromechanischem Gangtrainer*
  Die Evidenz, bestehend aus zwei RCTs (subakut; n=104), ist unzureichend, um eine Überlegenheit einer Rehabilitation mit FES und elektromechanischem Gangtrainer im Vergleich zur Standardrehabilitation nachweisen zu können. Die Qualität der Evidenz wurde als sehr niedrig eingestuft.

gem. Elektrostimulationsprogramme: unzureichende Evidenz

- *Gemischte Elektrostimulationsprogramme (auch beim Gehen)*
  Die Evidenz, bestehend aus einem RCT (subakut; n=38), ist unzureichend, um eine Überlegenheit einer Rehabilitation mit gemischten Elektrostimulationsprogrammen im Vergleich zur Standardrehabilitation nachweisen zu können. Die Qualität der Evidenz wurde als sehr niedrig eingestuft.

Radfahren mit FES: unzureichende Evidenz

- *Fahrradtraining (Cycling) mit FES*
  Die Evidenz, bestehend aus vier RCTs (subakut und chronisch; n=168), ist unzureichend, um eine Überlegenheit einer Rehabilitation mit der FES während des Radfahrens im Vergleich zur Standardrehabilitation nachweisen zu können. Die Qualität der Evidenz wurde als sehr niedrig eingestuft.

Laufbandtraining mit FES: unzureichende Evidenz

- *Laufbandtraining mit FES*
  Die Evidenz, bestehend aus einem RCT (chronisch; n=32), ist unzureichend, um eine Überlegenheit einer Rehabilitation mit FES während des Laufbandtrainings im Vergleich zur Standardrehabilitation nachweisen zu können. Die Qualität der Evidenz wurde als niedrig eingestuft.

Klinischer Nutzen der roboterassistierten Rehabilitation und der funktionellen Elektrostimulation in der Schlaganfallrehabilitation der **oberen Extremitäten**

obere Extremitäten: AWMF LL 2020

Die Aussagen zu den Ergebnissen basieren auf der AWMF S3 Leitlinie 2020. Die AWMF S3 Leitlinie identifizierte hierbei Evidenz, bestehend aus einem Cochrane-Bericht (45 RCTs; n=1.619) und 16 RCTs für die RAR, die die Einschlusskriterien erfüllten.

RAR für Armreha: 1 Cochrane SR und 16 RCTs

Die Primärstudien untersuchten die RAR zur Unterstützung der Schulter- und Ellbogenbewegungen (13 RCTs; subakut und chronisch; n=1,393), Unterarm- und Handgelenk RAR (1 RCT; chronisch; n=20) und RAR zur Rehabilitation der Fingerbewegungen (1 RCT; subakut und chronisch; n=21). Ein weiteres RCT (chronisch; n=127) beschrieb die verwendeten Roboter unzureichend.

FES für Armreha: 9 RCTs

Die AWMF S3 Leitlinie 2020 identifizierte überdies neun – den Einschlusskriterien entsprechenden – RCTs (subakut und chronisch; n=237) für die FES.

Evidenz deutet auf:

Hinsichtlich der Anwendung der zu evaluierenden Interventionen bei der Rehabilitation der oberen Extremitäten fand die AWMF S3 Leitlinie:

Zusatznutzen der RAR in subakutem Stadium hin

- Hohe Qualität der Evidenz, die auf einen Zusatznutzen der **RAR** für die Armrehabilitation von Schlaganfallpatient*innen im subakuten Stadium hindeutet.

- Niedrige Qualität der Evidenz für einen Zusatznutzen der **RAR** wurde bei Schlaganfallpatient*innen im chronischen Stadium gefunden.
- Niedrige Qualität der Evidenz wurde dafür gefunden, dass die **FES** in manchen Szenarien angewendet werden kann (z. B. bei Patient*innen mit schweren inkompletten Handparesen und teilweise erhaltener proximaler Motorik).

RAR chronisch und FES: unzureichende Evidenz

Laufende Studien

Gegenwärtig gibt es zahlreiche laufende Studien, die den Nutzen der RAR oder FES für die Schlaganfallrehabilitation evaluieren. Es wurden 24 RCTs für die RAR und sechs RCTs für die FES identifiziert.

24 laufende Studien

Limitationen

Die Aussagen der Evidenz zum Zusatznutzen der beiden Interventionen bei unteren und oberen Extremitäten wurde durch folgende Faktoren eingeschränkt:

Limitationen:

- Es gibt derzeit eine Vielzahl an verfügbaren Geräten mit gewissen Unklarheiten im Hinblick auf die Unterschiede der spezifischen Modalitäten der Interventionen.

Vielzahl an verfügbaren Geräten; Heterogenität der Produkte?

- Studien innerhalb der Schlaganfallrehabilitation verwenden verschiedenste Instrumente zur Messung der entscheidenden Endpunkte (eine standardisierte Messung in klinischen Studien ist erwünscht; jedoch tatsächlich noch nicht Realität).

Endpunktmessung innerhalb der Studien nicht standardisiert

- Die Evaluierung der Sicherheit von RAR und FES war aufgrund unzureichend standardisierter Berichterstattung der eingeschlossenen Studien stark limitiert.

Sicherheitsevaluierung: oft schlechtes Reporting in Studien

Schlussfolgerung

Die verfügbare Evidenz deutet darauf hin, dass manche Arten der roboterassistierten Rehabilitation (in Kombination mit der Standardrehabilitation) im Vergleich zur Standardrehabilitation allein in Abhängigkeit vom Schwergrad des Defizits einen klinischen Zusatznutzen bei Patient*innen mit Hemiparesen nach Schlaganfällen (subakute Phase) erbringen können. Die Evidenz ist unzureichend, um eine Überlegenheit der funktionellen Elektrostimulation (in Kombination mit der Standardrehabilitation) im Vergleich zur Standardrehabilitation allein zu zeigen.

Evidenz deutet auf Zusatznutzen der RAR hin; FES: unzureichende Evidenz

Angesichts der im Zuge der Schlaganfallrehabilitation zahlreichen Handlungsoptionen, des nur begrenzt nachgewiesenen Zusatznutzens, aber höherer Kosten mancher Interventionen sind gesundheitsökonomische Evaluationen für jene Interventionen zu empfehlen, die einen gewissen klinischen Nutzen oder zumindest keine Unterlegenheit vorweisen können. Hierbei sollte die (zeitliche wie physische) Entlastung der Physiotherapeut*innen im Zentrum stehen.

gesundheits-ökonomische Evaluierung empfohlen

Desinvestition erwägen (bei Int. ohne Nutzennachweis)

Für eine solche Evaluierung ist die Berücksichtigung der Rahmenbedingungen bzw. des organisatorischen Settings und der Schweregrad des Schlaganfalls unerlässlich. Andererseits sollte eine Desinvestition in Behandlungsmodalitäten, die nicht durch Evidenz belegt oder nicht kosteneffektiv sind, erwogen werden.

1 Introduction

Technological support in neurological rehabilitation of patients after stroke has become a matter of interest in recent years. The expectations are to unburden staff (e.g. physiotherapists) and to achieve better and faster clinical improvement.

technologische Unterstützung bei Rehab nach Schlaganfall

It is unclear whether and which of the many technological support systems (such as robotic assisted rehabilitation or different functional electrical stimulation systems) have proven effects based on clinical studies and which effects can to be expected. This systematic review is, therefore, aiming at answering the question on the effectiveness and safety of the many technological support systems in neurological rehabilitation of patients after stroke suffering from hemiparesis.

Erwartungen an Entlastung und bessere Therapieerfolge

Review: Evidenz

1.1 Robotics and functional electrical stimulation: Description and technical characteristics of technology

Robotics for stroke rehabilitation[1]

Robotic assisted rehabilitation (RAR) can be used to facilitate passive range of motion and support maintaining both range and flexibility [1, 2]. Robotic devices can be split into the following categories [3]:

Roboter-assistierte Rehabilitation:

- mobile/portable exoskeletons,
- "static"/stationary exoskeletons or body weight support (BWS) exoskeletons, and
- end-effector devices

mobile/portable Exoskelette

Stationäre Exoskelette

End-Effektoren

The most notable difference between end-effector devices and exoskeletons is that the patients are externally connected versus outfitted (worn by the patient) with the robotic device respectively [1, 2]. Exoskeleton systems have a one-to-one correspondence between the target movement segment and the robot: a preprogramed trajectory helps to guide a single movement segment. Exoskeletons can be further categorized into unilateral and bilateral robots; that is, the robots can control single or multiple joints. End-effectors use footplates or handles to generate a limb movement in space and no direct patient-robot joint alignment is required [3]. Further differences of robotic devices for upper limb stroke rehabilitation are the specific movement the robot assists (e.g., shoulder/elbow, forearm/wrist or fingers) [4]. A visualisation of end-effectors and exoskeletons is depicted in Figure 1-1 and Figure 1-2 respectively.

Unterschiede: Arm vs. Beine;

extern verbunden vs. direkt getragen;

unilateral vs. bilateral, etc.

[1] CoreModel B001 – Features of the Technology: what are robotics and FES for stroke rehabilitation

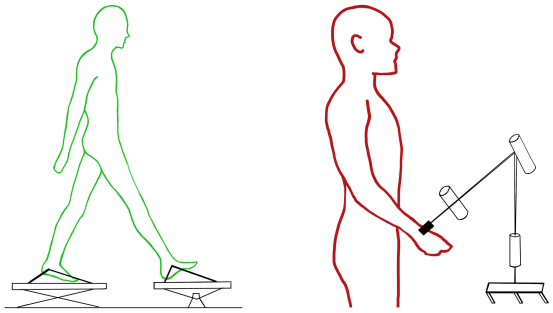

Figure 1-1: Illustrations of end-effector robotic devices, lower limb (left) and upper limb (right). Source: [3]

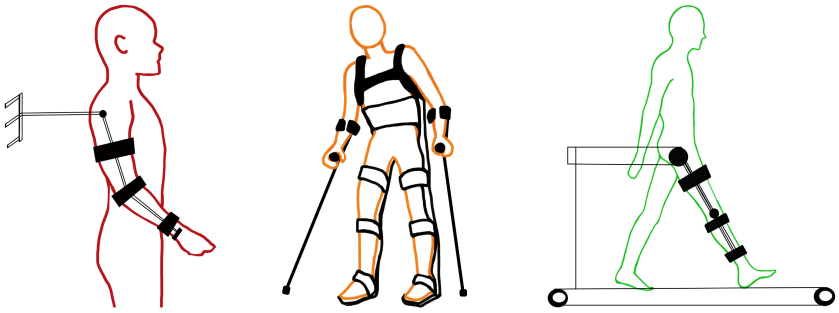

Figure 1-2: Illustration of exoskeleton devices (from left to right): upper limb exoskeleton, lower limb overground exoskeleton, lower limb body weight supported exoskeleton. Source: [3]

In this assessment, we were interested in all robotic electromechanical devices in which at least one segment is moved with technical (active) assistance:

Klassifikation nach Roboterkategorien nur bei UE

- For lower limb stroke rehabilitation, we categorised these devices into mobile exoskeletons, stationary exoskeletons, and end-effectors.
- For upper limb stroke rehabilitation, we did not subdivide these robotic-assisted active rehabilitation interventions further, since this report is based on a recent AWMF S3 guideline for upper limb stroke rehabilitation that did not cluster the evidence according to specific robots [4]. We did, however, cluster the robotic devices according to the movement the robot assists (e.g., shoulder/elbow, forearm/wrist or fingers).

15 Medizinprodukte als Unterstützung beim Gehtraining

For lower limb stroke rehabilitation, we have identified 15 different robotic devices aiming to improve/assist walking. Four and eight of these devices were static exoskeletons and portable exoskeletons respectively. Some further three devices were classified to be end-effectors. Table 1-1 gives an overview of available robotic devices for lower limb rehabilitation.

17 Medizinprodukte für Rehabilitation des Armes

For upper limb stroke rehabilitation, 17 robotic devices were identified. Of these, 14 focused on shoulder and arm training and further one and two robotic devices focused on forearm/wrist and finger movements respectively. We only found the approval status of six of these medical devices. Table 1-2 gives an overview of available robotic devices.

Table 1-1: Robotic devices for lower limb stroke rehabilitation

Product name (manufacturer)	Approval	DoF	Short description	Source
End-effectors				
G-EO System (Reha Technology AG)	FDA	n.a.	The G-EO System™ is a powered gait rehabilitation exoskeleton with a fixed frame. This wearable robot is capable of not only retraining correct walking but also stair climbing.	[5, 6]
Gait Trainer I and II (Medtec, Inc.)	FDA, CE	n.a.	The GT II offers intensive and repetitive locomotion therapy and is used for neurologic and orthopaedic patients.	[7]
LokoHelp (Woodway USA, Inc.)	n.a.	n.a.	The LokoHelp can be easily installed/removed on top of a treadmill and transmits the treadmill the movement of a patient. The device transmits the treadmill movement in order to lever on either side of the device. As a result, movement intimidating stance and swing phases of gait are hereby created.	[1]
Static exoskeleton systems				
Lokomat (Hocoma, Inc.)	FDA, CE	2 active	The Lokomat is a fixed (or stationary) exoskeleton that is used over a treadmill.	[1, 6]
Walkbot (P&S Mechatronics)	n.a.	n.a.	The Walkbot is a fixed frame gait rehabilitation exoskeleton.	[1, 8]
AutoAmbulator (HealthSouth Corp.)	FDA	n.a.	The AutoAmbulator provides the patient with a BWS treadmill training: The device has mechanically powered braces (to move the legs) and sensors that are used to track the patient's vital signs, movement as well as contact speed.	[1, 9]
Gait-Assistance Robot, GAR (Yaskawa Electric Corp.)	n.a.	n.a.	GAR uses four robotic arms, a full weight-bearing system as well as a foot pressure feedback system.	[10]
Exoskeleton Portable Devices				
Stride Management Assist, SMA (Honda Motor Co., Inc.)	FDA, CE	n.a.	The Stride Management Assist (SMA) device is a hip only powered exoskeleton. Its goal is to facilitate walking by providing additional force to swing the legs with each step.	[1, 11-13]
Hybrid Assistive Limb; HAL (Cyberdyne, Inc.)	CE	2 active	HAL uses EMG sensors to detect the intensity of patient's movement and assists gait training.	[6]
Bionic Leg (AlterG, Inc.)	n.a.	n.a.	The Bionic Leg is a powered exoskeleton to be used as a knee orthosis. The device detects the user's movements (through sensors, accelerometers and joint angle detectors) and provides mechanical assistance.	[1, 14]
Exo-Suit (ReWalk Robotics, Ltd.)	FDA, CE	n.a.	The Exo-Suit offers plantarflexion and dorsiflexion assistance synchronising with the patient's own gait adaptively to facilitate functional gait training.	[15]
Ekso GT (Ekso Bionics, Inc.)	FDA, CE	2 active, 1 passive	The Ekso GT is a hip-knee exoskeleton: the device detect the patient's intention of walking and swings his/her pelvis.	[6]
Indego (Parker Hannifin Corp.)	FDA, CE	n.a.	Indego® Therapy is an adjustable, lower-limb powered exoskeleton enabling individualized gait therapy for patients with lower extremity weakness or paralysis (such as complete/incomplete spinal cord injury and stroke).	[16, 17]
ExoAtlet II (ExoAtlet)	CE	n.a.	ExoAtlet II is a lower gait powered rehabilitation exoskeleton. It requires upper extremity strength in order to manage crutches and banlance and can be assisted with a tablet for medical operators and a further platform (the ExoCloud) provides doctors with user data.	[18, 19]
Anklebot (Bionik, Inc.)	FDA	2 active, 1 passive	The Anklebot is an exoskeleton in form of a knee brace that can be attached to a shoe. It works through adjusting forces that may strengthen the ankle and the lower extremity more broadly.	[1, 20]

Notes: the selection and classification of robotic devices and information on the approval status of the devices was informed by the following sources: [2, 6].

Abbreviations: CE – Conformité Européenne; BWS – body weight support; DoF – degrees of freedom; FDA – Food and Drug Administration; GAR – Gait-Assistance Robot; HAL – Hybrid Assistive Limb; n.a. – information not available.

Table 1-2: Robotic devices for upper limb stroke rehabilitation

Product name (manufacturer)	Type of Intervention	Approval	DoF	Short description	Source
Shoulder and elbow movements					
ARMin (n.a.)	Exoskeleton	n.a.	7	ARMin is used to improve motor function through task-specific, intensive training.	[2, 21, 22]
MIT MANUS (n.a.)	End-effector	n.a.	2	MIT MANUS assists both shoulder and elbow movement through guidance of the hand of the patient in the horizontal plane.	[2, 23]
MIME (Palo Alto Rehabilitation R&D Center)	End-effector	n.a.	6	MIME is a robotic arm that can be used unilaterally or bilaterally for shoulder and elbow rehabilitation.	[2, 23]
NeRoBot (N.A.)	End-effector	n.a.	3	The NeReBot is a cable-driven portable to be used when the patient is either prone or while sitting.	[2]
InMotionARM (Bionik, Inc.)	Exoskeleton	CE, FDA	n.a.	The InMotion ARM is a shoulder-elbow fixed/stationary rehabilitation exoskeleton with an optional extension for hand grasping.	[24, 25]
Pneu-Wrex (n.a.)	Exoskeleton	n.a.	n.a.	Pneu-Wrex is a lighweighted exoskeleton to be used as a pneumatically actuated orthosis, allowing wide range of motion of the arm.	[26]
GENTLE/S (Haptic Master)	End-effector	n.a.	3	GENTLE/S or the Haptic Master uses a haptic interface arm (incl. a wrist attachment mechanism) and two embedded computers: one monitor with a speaker and an overhead support system for the arm. GENTLE/s is used during task-oriented training: feedback is provided while being connected to the device by a wrist splint.	[2, 27]
Neuro-X system (Apsun Inc.)	End-effector	n.a.	2	Neuro-X system can support performing shoulder abduction and elbow-extension movements. The robot further provides feedback through a monitor	[2]
Arm Assist (TECNALIA R&I)	End-Effector	n.a.	n.a.	Arm Assist is a low-cost robotic system for rehabilitation of the shoulder and elbow post-stroke. The arm is supported through a device while playing interactive games.	[2, 28]
Arm Guide (n.a.)	End-effector	n.a.	3	The ARM Guide uses a motor and chain drive to move the user's hand along a linear rail, which assists reaching in a straight-line trajectory.	[2, 29]
Armeo Boom (Hocoma)	End-effector	FDA	3	Armeo Boom is a cable-driven manipulator specifically designed for the outpatient setting.	[2, 30, 31]
Armeo Power (Hocoma)	Exoskeleton	CE, FDA	6	The Armeo Power is used for early stage patients offering highly intensive arm rehabilitation.	[2, 31, 32]
ReoGo (Motorika Medical)	Endeffector	CE, FDA	2 active, 1 passive	The ReoGo is a stationary arm rehabilitation exoskeleton that comes on a small and compact wheeled platform. The end effector extension is capable of producing a wide range or reproducible movements in 3D space.	[2, 33]
UL-EX07 (n.a.)	Exoskeleton	n.a.	7	The UL-EX07 is a wearable robotic orthosis containing: an exoskeleton robot, control algorithms and virtual reality games that interact with UL-EX07.	[34]
Forearm and wrist movements					
Bi-Manu-Track (n.a.)	Endeffector	FDA	1	Bi-Manu-Track enables bilateral passive as well as active practice of forearm and wrist movement.	[2, 23]
Finger movements					
Hand Mentor (Kinetic Muscles Inc.)	Exoskeleton	FDA	n.a.	The Hand Mentor is a repetitive motion device designed for both clinical and home use. A Pneumatic artificial muscle is used to extend the fingers/wrist and electromyographic (EMG) biofeedback is provided by the device.	[35]
PneuGlove (Vinyl Technology Inc.)	Exoskeleton	n.a.	n.a.	The PneuGlove utilizes air pressure to provide assistance of digit extension in order to promote practice of hand movements, such as grasp-and-release tasks.	[36]

Notes: the selection and classification of robotic devices and information on the approval status of the devices was further informed by the following sources: [2, 6].

Abbreviations: CE – Conformité Européenne; DoF – degrees of freedom; FDA – Food and Drug Administration; n.a. – information not available.

Functional electrical stimulation

Funktionelle Elektrostimulation

FES is a targeted application of electrical stimulation inducing muscle contractions supporting motor activities. More precisely, FES integrates (neuromuscular) electrical stimulation with simultaneous functional movements through training or activities [1]. FES can be used in hemiparetic upper or lower extremity to improve functional ability through applying programmed burst of current to either a nerve or muscle in the affected extremity [1, 2].

programmierte Stromimpulse an Muskel

viele unterschiedliche Modalitäten:

There are numerous aspects and different modalities of electrostimulation after stroke. These depend, for instance, on whether the electrostimulation is used as a temporary therapy or as a neuro-prosthesis or neuro-orthesis. Subsequently and especially for lower limb rehabilitation, there are numerous interventions of electrostimulation. Generally, the interventions differ with regard to the following aspects [37]:

verschiedene Typen von Elektroden und Stimulationssysteme

- *Type of electrodes and stimulation system* (e.g., non-invasive systems with surface electrodes, systems with external stimulator and intramuscular wire electrodes, fully implanted systems with, inter alia, nerve cuff electrodes)
- *Number of stimulus channels* (1-8)
- *Stimulation target* (e.g., sensory and/or motor fibers in the peripheral nerve, motor nerve endings in the target muscle, different proximal/distal target muscles, Golgi tendon organs, flexor reflex afferences, acupuncture points, etc.)
- *Stimulation intensity*, especially motor subliminal (purely sensory) versus supra-threshold
- *Stimulation frequency*
- *Stimulation in a functional context* to support specific tasks/actions (e.g. step-synchronous while walking or on the bicycle ergometer) or while sitting/lying
- *Activity of the patient* (stimulation while patient actively contracts muscle or passive without individually induced muscle contractions)
- *Type of stimulation triggering* (cyclical process, sensor controlled, electromyogram triggered, triggered by patient or triggered by therapist)
- *Electrostimulation* alone or in combination with mechanical/electromechanical devices
- *Other differences* include the interval between the stimulation bursts, the duration of therapy, the therapeutic environment and study population (patients in the subacute/chronic stage)

Stimulationsfrequenz und -intensität, während des Gehens, im Sitzen, kombiniert mit Laufband oder Roboter, etc.

Fokus auf Elektrostimulation im funktionellen Kontext

In this assessment, only these types of electrostimulation are eligible that are used in the functional context to support specific tasks (i.e., during rehabilitative movements). Overall, we have identified eleven FES devices (of which eight have CE mark and/or FDA approval/clearance). Four devices can be used for upper limb stroke rehabilitation and further seven devices can be used for lower limb stroke rehabilitation. The FES devices still differ most notably between the type of electrodes (implanted or applied on the skin surface) and the number of stimulus channels (1-8). Table 1-3 gives a broad overview of the identified FES devices.

4 Medizinprodukte für OE, 7 für UE identifiziert

Table 1-3: FES devices for upper or lower limb stroke rehabilitation

Product name (manufacturer)	Approval	Short description	Source
	Lower limb		
Dropped Foot Stimulator (Odstock Medical Ltd)	FDA	The Dropped foot stimulator is 1-channel surface FES device for drop foot assistance	[38, 39]
Walkaide® (Accelerated Care Plus Corp.)[2]	FDA	Walkaide® is a 1-channel surface FES device for drop foot assistance	[38, 40]
NESS L300® (Bioness Inc.)	FDA,CE	The NESS L300 is a 1-channel surface FES device for drop foot assistance.	[38, 41]
ActiGait® (Otto Bock Healthcare Products GmbH)	CE	The ActiGait® system is an implanted 4-channel FES device for drop foot assistance.	[38, 40]
STIMuSTEP (Odstock Medical Ltd)	CE	The STIMuSTEP is an implantable 2 channel FES device for drop foot assistance.	[42]
RehaMove (Hasomed GmBH)	FDA, CE	The RehaMove is a 8-channel FES cycling system that can be installed on a stationary bike.	[43]
MyGait Stimulation System (Otto Bock Healthcare Products GmbH)	FDA	The stimulation system is intended to provide ankle dorsiflexion and knee flexion or extension in individuals with foot drop and thigh muscle weakness following an upper motor neuron injury or disease.	[44]
	Upper limb		
H200 (Bioness Inc.)[3]	FDA	The H200 is a 8-channel surface FES system	[38, 45]
MyndMove (n.a.)	FDA	MyndMove is a 8-channel surface FES system	[38]
Power-assisted FES system (OG GIKEN)	n.a.	The FES system by OG GIKEN is a portable 2 channel neuromuscular stimulator to be used for wrist and finger extension or shoulder flexion.	[46]
IVES (n.a.)	n.a.	The IVES device is a portable, noninvasive (surface), closed loop EMG-controlled, single-channel neuromuscular electrical stimulator.	[47]

Notes: Selection of devices was informed by [38, 48] and assisted by a manual web-based search. The list of FES devices is not exhaustive and limited to these devices for which at least some information was available that it can be used for stroke rehabilitation.
Abbreviations: CE – Conformité Européenne; FDA – Food and Drug Administration; n.a. – information not available.

CE Mark für viele Indikationen; hier: Fokus auf Pts mit Hemiparesen nach Schlaganfall

The technologies under investigation have numerous different possible indications[4]. We focus solely on post-stroke rehabilitation (lower extremities, upper extremities). This includes the rehabilitative use of these devices for hemiparetic post-stroke patients. Of note is that numerous devices for lower limb stroke rehabilitation are specifically designed for patients with drop foot (e.g., the drop foot stimulator by Oddstock Medical Inc.). Most of the devices under investigation received CE mark or FDA approval/clearance (see Table 1-1, Table 1-2, Table 1-3).

Kontraindikationen FES: bspw. Herzschrittmacher

For FES, there are further contraindications to be mentioned: cardiac and brain pacemakers, potentially life-threatening heart rhythm disturbances, epileptic seizures in the recent past, or metal implants [4].

Vorteile: RAR: Trainingsfrequenz und Intensität/Motivation sowie Entlastung der Physiotherapeut*innen

The use of robotic rehabilitation methods could have the advantage[5] of allowing more intensive and frequent therapy (by increasing the motivation to train), which at the same time reduces the effort of the physiotherapist [49]. In addition, exoskeletons for lower limb rehabilitation, for example when used for gait training, provide control strategies that support the stepping move-

[2] The WalkAide® device was launched by Hangar Inc. [38]

[3] Former: NESS Handmaster

[4] A0020 – For which indications have robotics and FES received marketing authorisation or CE marking?

[5] B0002 – What is the claimed benefit of robotics and FES for stroke rehabilitation in relation to standard rehabilitation?

ment only when they detect an appropriate lateral weight shift. Therefore, active user involvement, such as foot placement, is required [50].

FES: Stärkung der Muskel, Verbesserung der Blutzirkulation, Bewegungsfreiheit, Reduktion der Spastizität

The principle idea of FES is that the produced coordinated muscle contractions may increase the functional ability through strengthening the muscle and improve blood circulation or blood flow [51]. Yet, there are further mechanisms of a potential benefit: FES could also improve both flexibility and range of motion of the hemiparetic limbs or joints and reduce spasticity in the affected limb [48].

viele Geräte mit CE Zertifizierung oder FDA Zulassung

Most of the approved robotic and FES devices for stroke rehabilitation are categorized with moderate risk (class II) by the FDA [52-54][6]. Moderate risk devices are subject to less strict oversight by the FDA (or by CE certification): if medical devices are "substantially similar" to already approved devices, less rigorous clinical testing is required (e.g., through the 510k clearance possibility). This could explain that there are numerous currently available devices in the context of FES and robotic devices for stroke rehabilitation [54].

Setting: stationär oder ambulant

The use of RAR and FES can either be provided in the inpatient setting or in the outpatient setting by healthcare professionals[7]. Most of the medical devices assist the standard rehabilitation of stroke patients, but some of devices such as foot drop stimulators can also replace other rehabilitation tools such as an ankle-foot orthosis (AFO).

Einschulung der Physiotherapeut*innen und ggf. andere Kombinationsgeräte erforderlich

Depending on the specific device, the physiotherapist or other personnel working in stroke rehabilitation needs to be trained how to use these robotic devices or FES for stroke rehabilitation. Further, for some robotic devices, a treadmill is required [4, 37][8].

in Ö nicht in Standardrehabilitation inkludiert

Neither RAR nor FES are directly part of the "standard rehabilitation" program following stroke[9].

Unterschiede bei Ressourcen in Rehabilitationseinrichtungen

In this context, it must be noted that the rehabilitation programs including (available) resources used in specific rehabilitation centres may vary – also depending on the severity and chronicity of the stroke (see [55] and 1.2 Health problem and current use). Based on an expert consultation, some robotic devices and electrotherapy are already in use for stroke rehabilitation in rehabilitation centres in Austria.

[6] B0003 – What is the phase of development and implementation of robotics and FES for stroke rehabilitation?

[7] B0004 – Who administers robotics and FES for stroke rehabilitation and in what context and level of care are they provided?

[8] B0008 – What kind of special premises are needed to use robotics and FES? B0009: What supplies are needed to use robotics and FES for stroke rehabilitation?

[9] Reimbursement status: A0021 – What is the reimbursement status of robotics and FES for stroke rehabilitation?

1.2 Health problem and current use of technologies

Lähmungen und Funktionseinschränkungen nach Schlaganfall

The functional abilities of lower or upper extremities are often impaired in post-stroke patients due to a hemiparesis[10]. Improving walking and everyday activities are therefore important rehabilitation goals for post-stroke patients [37, 56, 57].

RAR und FES als Unterstützung zur Standardrehabilitation

The purpose of using robotics and FES in stroke rehabilitation is to support classical standard rehabilitation eventually leading to better functional outcomes for post-stroke patients: in the context of robotic devices this means offering more intense and frequent therapies and reducing the effort of physical therapists [49]. In the context of FES, the aim is to strengthen the muscle and improve blood circulation or blood flow [51].

Stadien nach Schlaganfall: akut: bis 3 Wochen subakut: bis 6 Monate chronisch: nach 6 Monate

A stroke is a neurological deficit that is caused by an acute focal injury of the central nervous system [58][11]. There are three main phases after a stroke: acute, subacute and chronic. In the acute phase of stroke (up to three weeks post-stroke) diagnostic, potential acute intervention and stabilization has the highest priority. In the subacute phase of stroke (up to six months post-stroke), the main focus is the recovery of functional and activity-related training. In a pathophysiological context, this time is characterized by the post-lesional plasticity; that is, changes (e.g., improvements) with regard to function and activitiy of post-stroke patients are observed especially in this time period. In the chronic phase of stroke (after six months post-stroke), changes with regard to function and activity level are still possible but the process of rehabilitation is – alike with healthy individuals with impairments – considered to be a "new learning" instead of a "re-learning" of independent walking and ADL [37, 59].

Hemiparese führt häufig zu funktionellen Schwierigkeiten, Fußhebeschwäche, etc.

After a stroke, a hemiparesis or foot drop can cause difficulties in the functional ability. A hemiparesis refers broadly to the weakness/inability to voluntary control movements on one side of the body and can occur after a stroke. A foot drop can further occur due to weakness of the muscle that normally lifts a foot, leading to the inability for patients to lift the front part of the foot [60, 61].

The side of the weakness is determined by where the stroke occurred in the brain. If the left side of the brain is injured, a right-sided weakness can occur and vice versa. A hemiparesis can cause the following impairments [60]:

- Loss of balance
- limitations in walking and moving around
- limitations in carrying, moving and handling objects
- Decrease in movement precision
- Muscle fatigue
- Lack of coordination

[10] Overview of the disease or health condition: A0001 – For which health conditions, and for what purposes are RAR and FES for stroke rehabilitation used?

[11] A0002 – What is stroke/post-stroke impairment in the scope of this assessment?

Risikofaktoren für Schlaganfall: hoher Blutdruck, Diabetes, Herzerkrankungen, Alter, etc.

The main risk factors of stroke are high blood pressure, diabetes, heart and blood vessel diseases, high LDL cholesterol levels, smoking, brain aneurysms, infections or other conditions causing inflammation, age, sex, ethnicity as well as family history and genetics[12]. Further risk factors include high stress levels and anxiety/depression, air pollution, medical conditions such as sleep apnea, medicines such as blood thinners, unhealthy lifestyle or overweight and obesity [62]. There are further known factors that affect the likelihood of stroke recovery: these risk factors for a poor recovery and lasting hemiparesis are the duration of the paresis and functional impairment as well as the extent of previous general impairment (e.g., previous strokes, orthopaedic diseases, amputations requiring prosthesis fitting) [37, 63, 64].

Dauer der Hemiparese beeinflusst Rehabilitationserfolg

Funktionalitätsaufbau innerhalb der ersten 72 Std. nach Schlaganfall ist essentiell

For lower limb stroke hemiparesis, for instance, the functional level up to 72 hours after stroke onset is essential: it is estimated that the probability of ambulating independently after six months is only 27% in patients that could not maintain sitting balance (for 30 seconds) and perform muscle contraction after this post-stroke time period. Conversely, patients who reached this functional level within 72 hours post-stroke are estimated to have a probability of independently ambulating of 98% [65, 66].

größter Fortschritt der Schlaganfallrehabilitation innerhalb der ersten 6 Monate

The exact pattern of damage is decisively influenced by the location and the size of the lesion. The most common is an infarction in the area served by the cerebral artery. In this scenario, hemiplegia usually affects mostly the arm and the face, leading to a better prognosis to improve leg function and relearning of walking in comparison to effectively rehabilitate arm function [37, 59]. The largest part of stroke recovery is achieved after six months[13]. The forecast regarding independent walking and ADL is unfavourable if there is no significant recovery within this period after stroke onset [37, 63, 64]. Six month post-stroke, about 50% of survivors still suffer from a hemiparesis and some 31% are unable to walk unassisted. Sensory deficits being an essential aspect for activities of daily living are prevalent in about 15% after their first stroke onset [65].

jährlich ca. 25.000 Schlaganfälle in Ö

In Austria, approximately 25,000 inhabitants suffer from a stroke each year. Additionally, strokes are the third most frequent cause of death, with 1.9% and 1.4% of deaths being attributable to a stroke in women and men respectively [67].

Gesundheitslast in Ö 2016: 68.883 DALYs und 3.888 Tote

Hence, stroke is a leading cause of mortality and disability. In Austria, the disability adjusted life years (DALYs) due to stroke were estimated to be 68,833 (95% CI: 59,863-77,120) and 3,888 deaths (95% CI: 3,361 to 4,500) occurred due to stroke in 2016. Further, the age-standardised rate of deaths due to stroke was estimated to be 72.2 per 100,000 in Austria respectively [68][14].

Diagnostik: Anamnese, körperliche und neurologische Untersuchung, CT/MRI

A diagnosis of stroke is based on the medical history, physical and neurological examination, laboratory (blood) test, computed tomography/magnetic resonance imaging scans as well as other diagnostic tests that can be further needed [69][15].

---

12 A0003 – What are the known risk factors for stroke (recovery)?

13 A0004 – What is the natural course of post-stroke hemiparesis?

14 Effects of the disease or health condition on the individual and society
A0005 – What is the burden of disease for patients with stroke?
A0006 – What are the consequences of stroke for the society?

15 Current clinical management of the disease or health condition: A0024: How is stroke currently diagnosed according to published guidelines and in practice?

Diagnostic tests examine specifically how the brain works (e.g., how the blood supply functions). In so doing, the injured brain area can be outlined. There are essentially three main types of tests [69]:

- *Imaging tests:* a picture of the brain will be created (similar to X-rays)
- *Electrical tests*: electrical impulses of the brain will be recorded
- *Blood flow tests:* these tests can show problems with regard to the blood flow to the brain

Grad der Beeinträchtung: körperliche Untersuchung, Tests der Funktionalität (versch. Instrumente)

Diagnosing the degree of impairment is an important task during the rehabilitation process [4]. Hence, the severity of impairment is assessed during the physical examination. For hemiparesis affecting the lower extremities (incl. foot drop), the physician will assess muscle power and endurance, control of voluntary movements and gait patterns as well as the capacity to maintain/change positions such as sitting to standing. In some cases, other tests such as X-rays may be required [70]. For hemiparesis affecting the upper extremities, the ADL and other functional abilities are assessed. There are several scientific instruments to measure these functional deficits; a broad description of these can be found in section 3.1 and section 4.1.

Rehabilitation hat hohen Stellenwert nach Schlaganfall

Generally speaking, rehabilitation has a high priority after a stroke[16]: it is usually started early after the incidence. The main rehabilitation goal is to maintain, relearn or to regain physical as well as mental abilities. In most cases, rehabilitation measures are continued after the hospital stay. Rehabilitation is often combined with an inpatient stay at the rehabilitation clinic. In the case of only mild or moderate strokes and in long-term management, rehabilitation can be carried out on an outpatient basis, i.e. from home if available [55].

multi-disziplinäres Team

verschiedenste Möglichkeiten der Rehabilitation, angepasst an Bedarf, Bedürfnisse und Beeinträchtigung der Patient*innen

Stroke rehabilitation is usually supervised by a team of different specialists, including doctors, physiotherapists, nursing staff, social workers, occupational therapists, speech therapists and, if necessary, other professional groups [55]. Targeted rehabilitation interventions aim to promote the recovery of disorders caused by the stroke [4, 37, 55, 71]. This includes, for example, walking exercises or strength training of paralyzed muscle groups. Possibly affected cognitive functions are also included in the rehabilitation program. Under the supervision of a speech therapist, language training can be provided. In addition, affected patients often suffer from anxiety, restlessness or a depressive disposition, in which psychological support can be further helpful [55]. Occupational therapists focus on self-care activities and use of aids, devices and strategies for successful managing daily routine. Such measures are individually tailored to the patient's need and impairment [55].

Ziel ist das (Wieder-)erlernen der Aktivitäten, die im Alltag benötigt werden: gehen, greifen, etc.

For gait rehabilitation, movement, balance and coordination problems are assessed and treated as part of the physiotherapy. Patients receive training and exercises designed to facilitate locomotion, getting up from a bed or chair and walk safely [37, 55]. If necessary, relatives are also instructed on how to train with the affected persons and support them in regaining the above-mentioned abilities [55].

[16] A0025 – How is stroke currently managed according to published guidelines and in practice?

An AWMF S2 guideline [37] recommends diverse rehabilitation measures in 2016. To improve or re-learn the **ability to walk** in post-stroke patients, the following rehabilitation interventions are recommended (recommendations A or B only):

AWMF S2 LL empfiehlt (Gehfähigkeit) v.a.

- Intensive gait training, if available and feasible including the gait trainer for subacute stroke patients who are not initially able to walk (Grade of recommendation: B)
- Intensive gait training: conventional or including the treadmill (as progressive as possible) for subacute stroke patients who are restricted in their walking ability (Grade of recommendation: B)
- For patients with spastic equinovarus deformity: injection of Botulinum Toxin A to reduce the use of other rehabilitation tools (Grade of recommendation: B)

intensives Gehtraining falls verfügbar mit Gangtrainer (bei nicht gehfähigen Pts) und konventionell oder mit Laufband (bei eingeschränkt gehfähigen Pts)
ggf. Injektion von bei Botulinum Toxin A bei Pts im chronischen Stadium

To improve the **gait speed** of post-stroke patients, the same guideline [37] recommends the following rehabilitation measures (recommendations A or B only):

Gehgeschwindigkeit:

- Task-based progressive endurance training (in implementation treadmill or progressive circuit training) in subacute stroke patients (grade of recommendation: A)
- Intensive gait training without a treadmill or intensive gait training including a treadmill or intensive supervised home exercise program (strengthening, endurance, balance) with progression, gait training with stimulation of flexor reflex afferences, and (additionally) leg function training in subacute stroke patients (grade of recommendation: B)
- Orthosis with or without electrostimulation in chronic stroke patients (grade of recommendation: B)

v. a. aufgabenbezogenes progressives Ausdauertraining

For a potential improvement of the **gait distance**, the AMWF S2 guideline [37] recommends similar rehabilitation techniques (recommendations A or B only):

Gehstrecke:

- Task-based progressive endurance training for subacute stroke patients (grade of recommendation: A)
- Intensive supervised home exercise program (strength, endurance, balance) with progression, and progressive gait training with a treadmill for subacute stroke patients (grade of recommendation: B)
- Task-related endurance training, e.g. progressive aerobic treadmill training and orthosis with electrostimulation (indirect effect) for chronic stroke patients (grade of recommendation B)

v. a. aufgabenbezogenes progressives Ausdauertraining

Finally, the AWMF S2 guideline [37] recommends the following rehabilitation measures to improve **balance** (recommendations A or B only):

Stärkung der Balance:

- Intensive walking training without a treadmill, intensive walking training including a treadmill or intensive supervised home exercise program (strength, endurance, balance) with progression and motor relearning programs for subacute stroke patients (grade of recommendation: B)

u. a. durch intensives Gehtraining ohne oder mit Laufband/Heimübungsprogramm, etc.

Similarly, the guideline [72] by the American Heart Association (AHA) recommends the following rehabilitation interventions to improve mobility of post-stroke patients (Class I recommendations; LoE: A):

mögliche Interventionen nach AHA für untere Extremitäten:

- Intensive, repetitive, mobility- task training in all patients with gait limitations
- AFO in patients with remediable gait impairments such as a drop foot

Aufgabentraining, Sprunggelenks-Orthesen, Gruppentherapie mit Zirkeltraining, etc.

The same guideline [72] judged the following rehabilitation measures to be reasonable to consider in 2016 (class IIa, LoE: A):

- Group therapy with circuit training
- Incorporating cardiovascular exercise and strengthening interventions
- Neuromuscular electrical stimulation (NMES) as an alternative to AFO for patients with foot drop

The AHA [72] further states that other rehabilitation measures such as treadmill training (with or without body-weight support) or overground walking exercise, robot-assisted movement training and mechanically assisted walking may be considered, but the usefulness/efficacy is less well established by evidence or opinion (Class IIb, LoE A)[17].

obere Extremitäten: Ergotherapie, Physiotherapie

For ADL, occupational therapists support stroke patients by giving instructions and practical training so that the affected patients are able to relearn or regain the ability to conduct everyday tasks. These may include eating, showering, dressing, cooking or writing. The rehabilitation is designed in a way that helps the patient to find alternate procedures, if the conventional way of one daily activity can no longer be carried out [55].

AWMF S3 Leitlinie aus 2020:

For rehabilitation of arm paresis after stroke, a recent AWMF S3 guideline [4, 71] concludes that there are also numerous interventions available, sometimes alternative, treatment modalities. The treatment is tailored to the specific needs of a patient and hence, the key of a suitable rehabilitation program is to neither demand too little nor to overexert the capabilities of the individual stroke patient. It is further essential that the stroke patients concentrate on specific aspects with regard to control of voluntary movements, carrying out tailored training at high doses and repetition [71].

The following treatment modalities are hereby highlighted by the guideline [71]:

Intensität und Organisationsform

Intensity and organisational form [4, 71]: If a faster recovery of arm activities is desired in subacute stroke patients, the AWMF S3 guideline recommends 30 minutes of specific therapy per day. Specific arm training can last for up to two to three hours per day to increase the effect on movement selectivity and arm activity. In later phases after stroke, depending on the individual treatment goals, structured repetitive training for 90-270 minutes per week may be useful to achieve further functional improvements. It is essential that the rehabilitation is very well structured and regularly supervised. Besides individual treatment, the specific training can, for instance, also be carried out in group setting or as a self-training at home (i.e., telerehabilitation).

Behandlung ohne Einsatz von Geräten: viele Geräte als mögliche Unterstützung

Treatment without the use of equipment [4, 71]: The AWMF S3 guideline recommends that impairment oriented training should be part of the standard treatment offered to subacute patients with severe paresis if an improvement of selective mobility is intended. For patients with mild arm paresis, arm-ability training should be included in the sub-acute stage to increase performance of the sensorimotor system if this is the focus of the treatment. Further, the AWMF S3 guideline highlights that task-oriented training, cognitive sensorimotor training, functional strength training, mirror training, mental self-training and constraint-induced movement training can be useful in specific contexts.

[17] It must be noted that class II recommendations indicate more broadly that there is conflicting evidence and/or divergence of opinion with regard to the usefulness/efficacy of the procedure [80].

Non-motorized, mechanical therapy devices [4, 71]: The AWMF S3 guideline states that there is a variety of different devices without the use of a motorized equipment. All of these devices aim at supporting repetitive arm movement. These include "BATRAC: bilateral arm training with rhythmic auditory cueing" or the "Rehaslide", arm ergometers or other devices. These can especially be offered to patients with severe arm paresis in the subacute stadium to support active hand and arm function. These can further be combined with virtual reality.

mechanische Therapiemittel zur Unterstützung bei repetitiven Armbewegungen

RAR [4, 71]: In case of severe arm paresis (especially in the subacute stadium of stroke), RAR is considered to be a useful therapeutic supplement if it is possible to implement it organizationally. RAR allows patients to practice specific movements with high repetition rates. Depending on the specific device, supporting the rehabilitation of shoulder and elbow movements, forearm and wrist movements or finger movements are possible. In the chronic phase of stroke, the AWMF S3 guideline states that RAR can be offered for these indications.

Arm-Robot-Therapie: v. a. bei Pts mit schweren Armparesen empfohlen, wenn organisatorisch möglich

Electrostimulation [4, 71]: Neuromuscular electrostimulation is stated as an option only, highlighting that the evidence base demonstrating a clinical benefit is weak. Neuromuscular electrostimulation of the shoulder muscles in the subacute stadium for the treatment or prevention of subluxation or treatment of the wrist and finger extensors, if possible, EMG-triggered, in severe incomplete hand and finger paresis come hereby into consideration. For patients with severe incomplete hand paresis, but at least partially preserved proximal motor function with movement and holding function, multi-channel FES, enabling grasping and releasing by means of electrostimulation, can be offered for practicing everyday activities with the therapeutic goal of improving distal selective movement (hand and fingers).

Elektrostimulation lediglich als Option in LL erwähnt; Verweis auf schwache Evidenz für Nutzen

Non-invasive brain stimulation [4, 71]: The AWMF S3 guideline recommends the use of repetitive transcranial magnetic stimulation in patients in the subacute stadium of stroke. In chronic stroke patients, this treatment is not specifically recommended but stated as an option. According to the AWMF S3 guideline, however, the use of transcranial direct current therapy is currently not recommended (apart from clinical trials).

nicht-invasive Hirnstimulation: Empfehlung für rTMS

Drugs [4, 71]: Botulinum Toxin A is recommended by the AWMF S3 guideline especially in cases of severe paresis, affecting the ability to integrate the paralysed arm into everyday life (i.e. passive functions in a spastically relevant way). The use of Botulinum Toxin A could also have a beneficial effect on pain in the context of spastic paresis. The guideline further highlights that there are several drugs (e.g., L-Dopa, Fluoxetin und Cerebrolysin) with some evidence for improvement of functional recovery, especially in severe arm paresis. The guideline states, however, that Cerebrolysin is not approved/ available in Austria. For all other drugs (e.g., Donepezil, D amphetamine), the evidence does not justify its use in arm rehabilitation after stroke according to the AWMF S3 guideline [4, 71].

Medikamente: Empfehlung für Botulinum Toxin A

zur Förderung der motorischen Erholung

Taping and orthoses [4, 71]: According to the AWMF S3 guideline, wrist support splints or shoulder taping, for instance, can have a positive, possibly prophylactic effect on pain in the treated joints in severe arm paresis. This also applies to other supportive tools (such as the support cushion or a wheelchair table), preventing a severely paralyzed arm from hanging down. According to expert opinion, the guidelines recommend a basal consideration of these tools in arm rehabilitation following stroke. However, positioning orthoses

Taping und Orthesen: Empfehlung (Expertenmeinung), diese grundständig in Betracht ziehen

as well as taping of joints of affected centrally paretic arm do not promote active functional recovery. Hence, the guideline recommends that these treatment modalities should not be used for this purpose.

AHA Leiltinie empfiehlt u. a. aufgabenspezifisches Training

Training der Aktivitäten des Alltags: angepasst an Patient*in

For upper limb stroke rehabilitation the AHA guideline [72] recommends, similarly to the AWMF S3 guideline, the following rehabilitation measures (Class I only):

- *Task-specific training:* tasks are graded to challenge individual capabilities, practiced repeatedly, and progressed in difficulty on a frequent basis (LoE: A)
- *ADL training:* Therapy needs to be tailored to individual needs and eventual discharge setting (LoE: A)
- *Instrumental ADL training:* therapy needs to be tailored to individual needs and eventual discharge setting (LoE: A)

Further rehabilitation therapies were judged to be reasonable to consider in specific contexts (class IIa recommendation):

- Constrained induced movement therapy if patients are eligible (LoE: A)
- Robotic therapy (LoE: A) for patients with moderate to severe upper limb paresis (LoE: A)
- NMES for individuals with minimal volitional movement in post-stroke patients in the first few month of the incidence or in stroke patients with shoulder subluxation (LoE: A)
- Mental practice as adjunct upper limb rehabilitation services (LoE: A)
- Strengthening exercises as adjunct to functional task practice (LoE: B)
- Virtual reality as a method to deliver upper limb movement practice (LoE: B)

Some further two interventions were recommended (class IIb) by the AHA guideline [72]: somatosensory retraining in stroke patients with somatosensory loss (LoE: B) and bilateral training paradigms in upper limb rehabilitation (LoE: A) may be considered. Acupuncture is not recommended for the improvements of ADL in upper limb rehabilitation (Class III; LoE: A).

traditionelle Physiotherapie: z. B. sog. Bobath-Therapie

In clinical practice, “traditional” rehabilitation of physiotherapy may include Bobath-therapy or the proprioceptive neuromuscular facilitation [73]. In addition, [55], forced use of the affected hand/arm (constraint-induced movement therapy) and active practice of selective simple movements for high degree paresis may be seen as newer therapies in clinical practice [55].

It is to be noted that the rehabilitation of stroke is multimodal and different forms of therapy exist that may not be always be mutually exclusive. That is, multiple rehabilitation techniques can be used depending on the severity of impairment [73].

2 Methods

Kooperation mit ReMoS –Arbeitsgruppe in AWMF

The study was conducted in collaboration with the *Rehabilitation der Mobilität nach Schlaganfall* (ReMoS) working group that updated their *Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften* (AWMF) guideline concurrently [37]. For RAR, ReMoS were first authors for mobile exoskeletons (CD), stationary exoskeletons (HW) and end-effectors (KMS). The AIHTA (GG, MW) conducted the update systematic review for FES based on the evidence found in the initial guideline published in 2015 [37] and further systematically searched for new potentially eligible studies in the past two years for RAR.

The study was conducted in accordance with the PRISMA statement [74, 75]. The EUnetHTA Core Model was used flexibly as a reporting standard [76].

2.1 Research questions

PIKO-Fragen

- Is *robot assisted rehabilitation (RAR)* in comparison to standard rehabilitation alone in post-stroke patients with a hemiparesis of the *lower extremities* more effective and safe concerning ability to walk independently and adverse events?
- Is *functional electrical stimulation (FES) therapy* and standard rehabilitation in comparison to standard rehabilitation alone in post-stroke patients with a hemiparesis of the *lower extremities* more effective and safe concerning ability to walk independently and adverse events?
- Is *RAR* in comparison to standard rehabilitation alone in post-stroke patients with a hemiparesis of the *upper extremities* more effective and safe concerning activities of daily living (ADL) and adverse events?
- Is *FES* and standard rehabilitation in comparison to standard rehabilitation alone in post-stroke patients with s hemiparesis of the *upper extremities* more effective and safe concerning ADL and adverse events?

2.2 Inclusion criteria

Einschlusskriterien für relevante Studien untere Extremitäten: AWMF update zu RAR (2019-20), update zu FES (2012-20)

obere Extremitäten: Extraktion der Daten aus AWMF-S3 Leitlinie (2020)

For lower limb stroke rehabilitation, we have cooperated with the ReMoS working group (AWMF): we updated the evidence for lower limb RAR (2019-2020) and FES (2012-2020).

For upper limb stroke rehabilitation, we have identified a recent high quality AWMF S3 guideline choosing a similar PICO question [4]. Hence, our evidence synthesis on the topic is fully based on this guideline. The guideline included both RCTs and systematic reviews. For the RCTs identified by the AWMF S3 guideline, our inclusion criteria applied. Systematic reviews are not described, unless Cochrane reviews were identified by the AWMF S3 guideline. Inclusion criteria for relevant studies are summarized in Table 2-1–Table 2-4.

Table 2-1: Inclusion criteria for robot assisted rehabilitation in post-stroke patients suffering from lower limb hemiparesis

Population	Patients who have had a stroke and suffer from hemiparesis of lower extremities
Intervention	Rehabilitation with robotics (exoskeletons and end-effectors) assisting gait training
Control	Standard gait rehabilitation
Outcomes	
Efficacy	**Crucial:** ■ Ability to walk independently: e.g., Functional Ambulation Category (FAC) ■ Other functional outcomes such as gait distance, walking speed and balance **Relevant/secondary:** ■ Muscle strength: e.g., Motricity Index ■ Health related Quality of Life and patient satisfaction **Rationale:** Appropriate outcomes were informed by a manual search in the COMET database, identified literature [77] and Cochrane systematic reviews [78, 79]
Safety	■ Adverse events ■ Serious adverse events
Study design	Randomised controlled trials with at least 10 patients enrolled in each arm and acceptable quality (1b LoE)
Settings	Inpatient or outpatient care

Table 2-2: Inclusion criteria for FES in post-stroke patients suffering from lower limb hemiparesis

Population	Patients who have had a stroke and suffer from hemiparesis of lower extremities
Intervention	Functional electrical stimulation (FES) in combination with standard gait rehabilitation
Control	Standard gait rehabilitation
Outcomes	
Efficacy	**Crucial:** ■ Ability to walk independently: e.g., Functional Ambulation Category (FAC) ■ Other functional outcomes such as gait distance, walking speed and balance **Relevant/secondary:** ■ Muscle strength: e.g., Motricity Index ■ Health related Quality of Life and patient satisfaction **Rationale:** Appropriate outcomes were informed by a hand search in the COMET database, subsequent identified literature [77] and a systematic review [80]
Safety	■ Adverse events ■ Serious adverse events
Study design	Randomised controlled trials with at least 10 patients enrolled in each arm and acceptable quality (1b LoE)
Settings	Inpatient or outpatient care

Table 2-3: Inclusion criteria for rehabilitation with robot assisted rehabilitation in post-stroke patients suffering from upper limb hemiparesis

Population	Patients who have had a stroke and suffer from hemiparesis of upper extremities
Intervention	Arm rehabilitation with robotics (exoskeletons and end-effectors)
Control	Standard arm rehabilitation
Outcomes	
Efficacy	**Crucial:** ■ Activities of daily living (ADL): e.g., Barthel Index, Functional independence Measure **Relevant/secondary:** ■ Body function and structure: e.g., FM – motor arm and leg tool ■ Activity limitations: eg., Action Research Arm Test (ARAT) ■ Muscle strength: e.g., Motricity Index ■ Health related Quality of Life and patient satisfaction **Rationale:** Appropriate outcomes were informed by a hand search in the COMET database, identified literature [77] and Cochrane systematic reviews [78, 79]
Safety	■ Adverse events ■ Serious adverse events
Study design	Randomised controlled trials with at least 10 patients enrolled in each arm and acceptable quality (1b LoE)
Settings	Inpatient or outpatient care

Table 2-4: Inclusion criteria for FES in post-stroke patients suffering from upper limb hemiparesis

Population	Patients who have had a stroke and suffer from hemiparesis of upper extremities
Intervention	Functional electrical stimulation (FES) in combination with standard arm rehabilitation
Control	Standard arm rehabilitation
Outcomes	
Efficacy	**Crucial:** ■ Activities of daily living (ADL): e.g., Barthel Index, Functional independence Measure **Relevant/secondary:** ■ Body function and structure: e.g., FM – motor arm and leg tool ■ Activity limitations: eg., Action Research Arm Test (ARAT) ■ Muscle strength: e.g., Motricity Index ■ Health related Quality of Life and patient satisfaction **Rationale:** Appropriate outcomes were informed by a hand search in the COMET database, subsequent identified literature [77] and a systematic review [80]
Safety	■ Adverse events ■ Serious adverse events
Study design	Randomised controlled trials with at least 10 patients enrolled in each arm and acceptable quality (1b LoE)
Settings	Inpatient or outpatient care

2.3 Detailed research questions (according to EUnetHTA CoreModel)

Assessment elements from the EUnetHTA Core Model® for the production of Rapid Relative Effectiveness Assessments (Version 4.2) were customised to this assessment's specific objectives [173].

Description of the technology	
Element ID	**Research question**
B0001	What is the technology and the comparator(s)?
A0020	For which indications has the technology received marketing authorisation or CE marking?
B0002	What is the claimed benefit of the technology in relation to the comparators?
B0003	What is the phase of development and implementation of the technology and the comparator(s)?
B0004	Who administers the technology and the comparators and in what context and level of care are they provided?
B0008	What kind of special premises are needed to use the technology and the comparator(s)?
B0009	What supplies are needed to use the technology and the comparator(s)?
A0021	What is the reimbursement status of the technology?

Health problem and Current Use	
Element ID	**Research question**
A0001	For which health conditions, and for what purposes is the technology used?
A0002	What is the disease or health condition in the scope of this assessment?
A0003	What are the known risk factors for the disease or health condition?
A0004	What is the natural course of the disease or health condition?
A0005	What is the burden of disease for the patients with the disease or health condition?
A0006	What are the consequences of the disease or health condition for the society?
A0024	How is the disease or health condition currently diagnosed according to published guidelines and in practice?
A0025	How is the disease or health condition currently managed according to published guidelines and in practice?

Clinical Effectiveness	
Element ID	**Research question**
D0011	What is the effect of the technology on patients' body functions?
D0016	How does the use of technology affect activities of daily living?
D0012	What is the effect of the technology on generic health-related quality of life?
D0013	What is the effect of the technology on disease-specific quality of life?
D0017	Was the use of the technology worthwhile?

Safety	
Element ID	**Research question**
C0008	How safe is the technology in comparison to the comparator(s)?

2.4 Sources

systematische Literatursuche und gezielte Handsuche

Quellen: Leitlinien, UpToDate, DynaMed, manuelle Suche in PubMed

Description of the technology

- Manual search in PubMed for relevant literature
- Background publications identified in database search: see Section 2.5
- Exoskeleton Report: https://exoskeletonreport.com/
  - Manual web-based search to identify relevant literature

Health problem and Current Use

- UpToDate: https://www.uptodate.com/home
- DynaMed: www.dynamed.com
- DexiMed: https://deximed.de/intro
- Background publications identified in database search: see Section 2.5
- Hand search for treatment guidelines and epidemiologic data

Clinical effectiveness and safety

- Lower limb stroke rehabilitation: systematic and hand search (see 2.5 Systematic literature search)
- Upper limb stroke rehabilitation: Recent AWMF S3 guideline published in 08/2020 [4]

2.5 Systematic literature search

systematische Literatursuche in 5 Datenbanken

The systematic literature search was conducted in May 2020 in the following databases:

- Medline via Ovid
- Embase
- The Cochrane Library
- CRD (DARE, NHS-EED, HTA)
- PEDro

identifizierte Publikationen (insg.):
Exoskelett: 1.425
FES: 1.331

After deduplication, overall 1,425 and 1,318 citations were identified for the RAR and FES search respectively. The specific search strategy employed can be found in the appendix (Literature search strategies robot assisted rehabilitation, Literature search strategies functional electrical stimulation for stroke rehabilitation). By hand-search, an additional 13 publications were found, resulting in overall 1,425 (RAR) and 1,331 (FES) hits.

Suche nach laufenden Studien:
RAR: 120
FES: 130

Furthermore, to identify ongoing and unpublished studies, a search in three clinical trials registries (ClinicalTrials.gov, WHO-ICTRP, EU Clinical Trials) was conducted in August 2020 resulting in 120 and 130 potentially relevant hits for RAR and FES respectively.

For upper limb rehabilitation, we did not conduct a further search for primary studies due to the identified recent guideline published in August 2020.

2.6 Flow chart of study selection

Lower limb stroke rehabilitation

Literaturauswahl der Update Suchen

For lower limb stroke rehabilitation, ReMoS identified 11 **RCTs** for RAR until early 2019 and further eleven RCTs for FES assisted stroke rehabilitation until 2012.

For RAR, our update search yielded 1,425 hits, of which 54 articles were eligible for full-text review. Of these, five RCTs were identified, but none of these fulfilled our inclusion criteria (LoE/level of evidence: 1b).

For FES assisted stroke rehabilitation, our update search yielded 1,331 potentially relevant hits, of which 229 articles were eligible for full-text review. Of these, 19 potentially relevant RCTs were identified. Of these, six RCTs (8 publications) were of acceptable quality (LoE: 1b).

The flow charts of the study selection process for robot and FES assisted stroke rehabilitation can be found in Figure 2-1 and Figure 2-2 respectively.

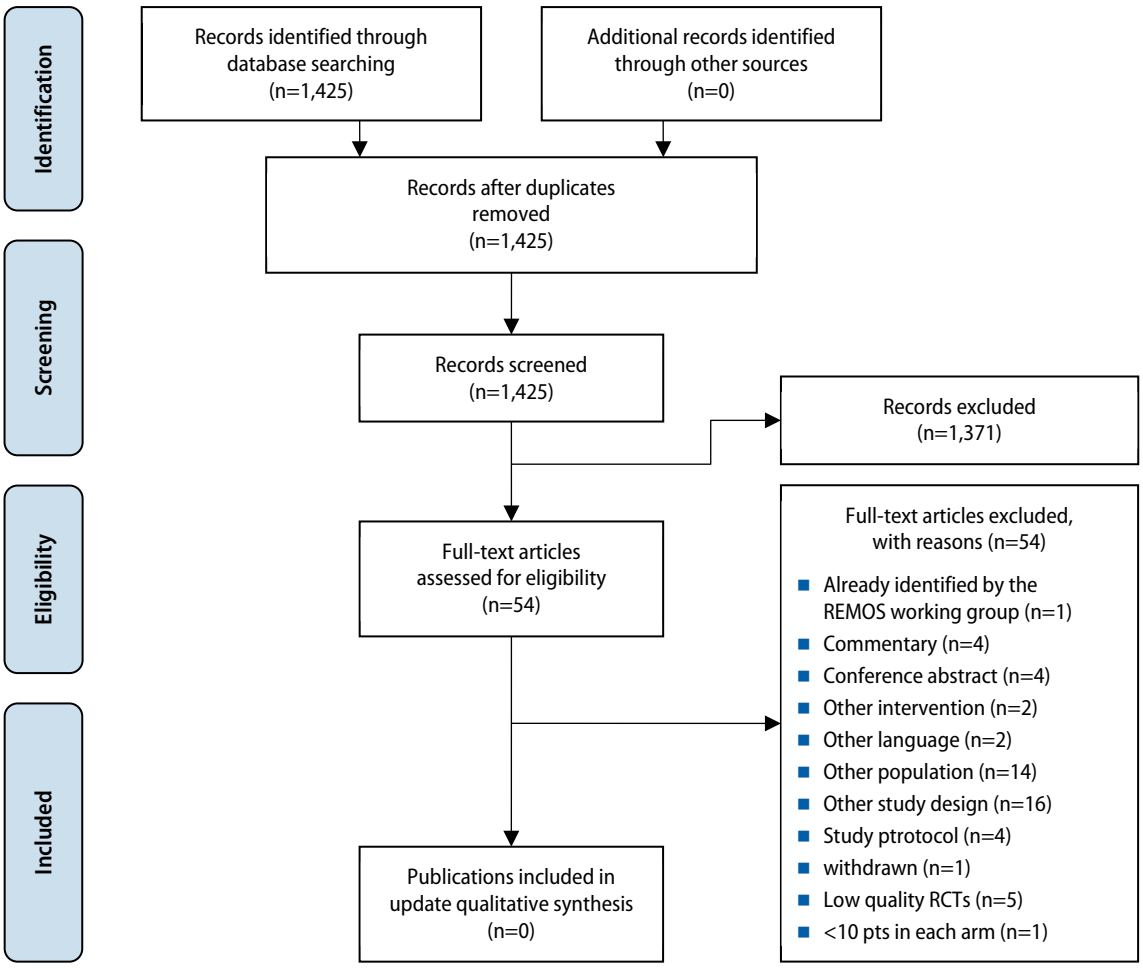

Figure 2-1: Flow chart of study selection for the update search on robot assisted lower limb stroke rehabilitation (PRISMA Flow Diagram)

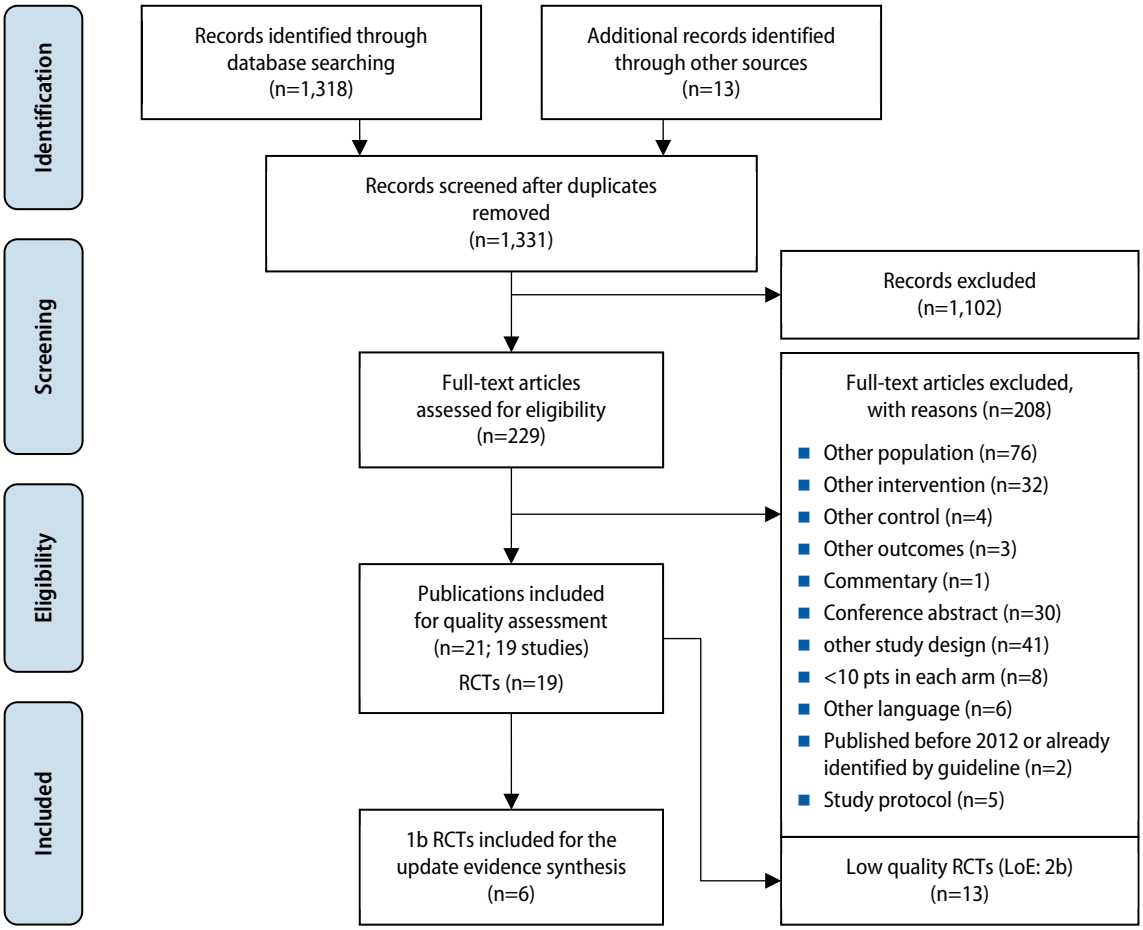

Figure 2-2: Flow chart of study selection for the update search on functional electrical stimulation for lower limb stroke rehabilitation (PRISMA Flow Diagram)

Upper limb stroke rehabilitation

The evidence synthesis of the recent AWMF S3 guideline [4] published in July 2020 was used to describe the effectiveness and safety of both robot and FES assisted stroke rehabilitation. Hence, no systematic search and study selection was needed.

2.7 Analysis

untere Extremitäten: Qualitätsbeurteilung der Studien mit der PEDro Scale

For lower limb stroke rehabilitation, two persons (GG, MW) systematically assessed the risk of bias (RoB) of the included studies of the update searches using a modified version of the Physiotherapy Evidence Database (PEDro) scale [81]. Based on the methodology of the initial guideline [37], the overall validity of the studies was classified (++, +, -, --) and subsequently categorised into 1b RCTs (++ or +) or 2b RCTs (- or --) according to the The Centre for Evidence-Based Medicine (CEBM) classification (see Table 2-5).

Datenextraktion aus Studien

Relevant data from eligible studies were systematically extracted into data-extraction tables: one person (GG) extracted the data, whilst another person (MW) controlled the extracted data.

obere Extremitäten: Qualitätsbeurteilung der LL mit der AGREE-II checklist; Datenextraktion aus LL

For upper limb stroke rehabilitation, two persons (KW, GG) assessed the quality of the identified recent guideline using the AGREE-II (Appraisal of Guidelines, Research and Evaluation) checklist [82]. To summarise the identified studies of the guideline, summary tables of the identified best available evidence (LoE: 1b) were created by KW (and controlled by GG) in accordance with the summary tables in the format of the ReMoS working group [37].

All discrepancies were resolved by consensus or by involving a third researcher (CW) in case it could not be resolved.

Table 2-5: Level of evidence according to the CEBM Classification

1a	Systematic reviews (with homogeneity) on the basis of randomized controlled trials
1b	Randomized controlled trials with narrow confidence interval
2a	Systematic reviews (with homogeneity) on the basis of non-randomized controlled studies (NRCTs) and prospective cohort studies (incl. low quality RCTs; e.g. < 80 follow-up)
2b	NRCTs or prospective cohort studies (including RCTs of lower quality; e.g. < 80 % follow-up)
3a	Systematic reviews (with homogeneity) on the basis of case-control studies, cross-sectional studies or retrospective cohort studies (including NRCTs and/or prospective cohort studies with low quality)
3b	Case-control studies, cross-sectional studies or retrospective Cohort studies (including NRCTs and/or prospective low quality cohort studies)
4	Case series (including case-control studies, cross-sectional studies or retrospective cohort studies of lower quality)
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"

Source: [83]

2.8 Synthesis

UE: qualitative Synthese der Evidenz; Zusammenfassung der Ergebnisse mit GRADE

For lower limb stroke rehabilitation, a qualitative synthesis of the evidence was performed in cooperation with the ReMoS working group [37]. We used GRADE (Grading of Recommendations, Assessment, Development and Evaluation) flexibly to synthesise the identified evidence [84]: GRADE evidence tables and summary tables in the format of the ReMoS working group that are influenced by GRADE [37] were hereby created.

OE: Beschreibung der LL-Evidenzsynthese

For upper limb stroke rehabilitation, the evidence synthesis is fully based on the identified AWMF S3 guideline [4].

3 Lower limb stroke rehabilitation

3.1 Outcomes

3.1.1 Clinical effectiveness

wesentliche Zielparameter:

Gehfähigkeit, Gehgeschwindigkeit, Gehstrecke, Balance

The following endpoints were selected as the crucial endpoints for assessing the effectiveness of RAR or FES in addition to standard care:

- Ability to walk (AtW)
- Walking speed (WS)
- Gait distance (GD)
- Balance (BAL)

weitere Endpunkte:

Muskelkraft, Patient*innenzufriedenheit, Lebensqualität

Further three outcomes were defined as relevant:

- Muscle strength (MS)
- Patient satisfaction (PSA)
- Health-related Quality of Life (HRQoL)

Gehfähigkeit mittels validierter Instrumente (keine Symmetriedaten)

Ability to walk (AtW) may be described as the most crucial outcome to evaluate the effectiveness of lower limb stroke rehabilitation. According to the AWMF guideline we have updated, the AtW can be measured by 25 different outcome instruments [37]. These include, for instance, the following:

- *Functional Ambulatory Category (FAC):* The FAC assesses the functional ambulation. Clinicians hereby complete a box of four broad categories with regard to walking ability. The patients are rated between 0 (patient cannot walk or needs help from at least 2 persons) and 5 (patient can walk independently, anywhere). It is a widely used instrument used during physical therapy [85].
- *Subtest of the Chedoke McMaster Disability Inventory (CMSA*): The CMSA assesses both physical impairment and disability. The subtest "Walking index" consists of five items covering walking ability in different scenarios, e.g., indoor, outdoor, stairs [86].
- *Clinical Outcomes Variable Scale (COVS):* The COVS is a computer-based instrument with an observer-based assessment type. It can be used to assess the functional mobility of post stroke patients [87].
- *Rivermead Mobility Index (RMI):* The RMI is primarily a self-reported tool, with 14 self-reported and one direct observation items. A maximum of 15 points can be reached, with higher scores indicating better mobility [88].

Gehgeschwindigkeit: z. B. 10 Meter Gehtest

Walking speed (WS) can, for instance, be measured with the 10 meter walking test or other diverse walking tests (e.g., 5 meter, 5.5 meter, etc.).

Gehstrecke: z. B. 6 Min. Gehtest

Gait distance (GD) can be measured by using the 6-minutes walk test (6MWT) or comparable tests that evaluate how far a person can walk in a certain time period.

Balance: Sturzgefahr, Stürze, Frakturen, klinische Skalen zur Standsicherheit

NICHT: Symmetriedaten, Kadenz, metabolische Werte, posturographische Parameter

Balance (BAL) is a further crucial endpoint: there are numerous scales available to evaluate the BAL of post-stroke patients [37]. These include, but are not limited to, the following instruments:

- *Berg Balance Scale (BBS):* The BBS assesses static balance and fall risk. A 14-item score can yield a maximum score of 56, with higher scores indicating better balance [89].
- *Timed Up and Go test (TUG):* The TUG determines the fall risk and measures the progress of balance (incl. sit to stand as well as walking). The assessor essentially observes the time a patient needs to stand up, with varying cut-off times to be found in clinical studies [90].

It is to be noted that all of the aforementioned endpoints may have some overlaps with others and the list of outcome instruments is not exhaustive. For a more detailed description, and a full list, of all eligible outcome instruments, the reader is referred to the AWMF guideline [37].

weitere/sekundäre Endpunkte: Muskelkraft: Motricity Index

Muscle strength (MS) was considered to be another relevant outcome as it may be regarded as an indirect measure of a rehabilitation success. This endpoint can, for instance, be measured with the Motricity Index (MI) [91].

Zufriedenheit und Lebensqualität mittels Fragebögen

For measuring patient satisfaction (PSA), there are various scientific tools available, however, we also considered discontinuation due to the study device or a simple visual analog scale measuring tolerance or acceptance as eligible for this outcome

Health-related Quality of Life (HRQoL) can be assessed with generic (e.g., EQ-5D-5L [92], SF-36 [93]) or stroke specific instruments; e.g., by using the Stroke Impact Scale (SIS).

3.1.2 Safety

Sicherheit: unerwünschte und schwerwiegende unerwünschte Nebenwirkungen

The following outcomes were selected to evaluate the safety of the rehabilitation devices under evaluation:

- Adverse events (AE)
- Serious adverse events (SAE)
- Device-related adverse events

The definitions of AEs/SAEs and device-related AEs/SAEs of the European Commission guidelines on medical devices were applied [94].

3.2 Effectiveness and safety of robot assisted lower limb stroke rehabilitation

This chapter is fully based on an evidence synthesis of an AWMF S2 guideline[18].

3.2.1 Included studies

Study characteristics

11 RCTs

For the evaluation of the clinical effectiveness and safety of robot assisted lower limb stroke rehabilitation, the AWMF S2 guideline included eleven studies [14, 95-104] that met our inclusion criteria.

nur 1b LoE

The LoE of the individual studies was judged to be 1b for all included individual studies (+ for all eleven studies).

3 Subinterventionen:

The interventions in the included studies differed with respect to specific modalities of robot assisted lower limb rehabilitation. The guideline structured these accordingly:

- **stationäre Exoskelette**

  Stationary exoskeletons: Four studies (subacute and chronic; n=211) evaluated the use of the Lokomat additionally to conventional gait training.

- **mobile Exoskelette**

  Mobile exoskeletons: One study evaluated the use of a HAL robot (subacute; n=28) and bionic leg (chronic; n=20) respectively.

- **stationäre Endeffektoren**

  Stationary end-effectors: Five studies (subacute and chronic; n=361) evaluated the use of end-effector assisted gait training additionally to conventional gait training.

The length of follow-up in the included studies ranged from two weeks to twelve months.

Patient characteristics, stroke stadium, and setting

Unterschiede in Stadium des Schlaganfalls und

Seven studies [95, 97-99, 102-104] enrolled patients in the subacute stadium of stroke and further four studies [14, 96, 100, 101] enrolled chronic stroke patients.

The severity/level of impairment was reported in nine out of eleven studies: Three studies [95, 97, 98] reported that patients needed to have a FAC of not more than two to be included. Another four studies [14, 96, 100, 103] included patients that were at least independent in their walking abilities (with support) or able to walk (e.g. 10 meters). The remaining studies [99, 101] included patients that were not able to walk, had significant, or had stabilised motor deficits.

Setting

The setting was reported in ten out of eleven studies: While seven studies [95-99, 103, 104] included stroke patients in the inpatient rehabilitation setting, the remaining three studies [14, 100, 102] evaluated RAR in the outpatient setting.

[18] As of March 2021, the guideline is not published and is estimated to be available in 2021.

3.2.2 Results

Stationary exoskeletons

stationäre Exoskelette vs. konventionelle Physiotherapie: 4 RCTs; keine stat. signifikanten Unterschiede in:

For **stationary exoskeletons**, four studies [95-98] compared robot assisted gait training (RAGT) to conventional physiotherapy or physiotherapy assisted locomotion training. Overall, there is moderate quality evidence that RAGT may not additionally improve AtW and BAL. Low quality evidence suggests that it may not additionally improve WS and GS.

Gehfähigkeit: Ø in 3 RCTs

AtW was reported in three studies (subacute; n=163): none of the studies found a statistically significant difference in AtW when comparing RAGT to conventional physiotherapy [95, 97, 98].

Gehgeschwindigkeit: Ø in 1 RCT

WS was reported in one study (chronic; n=48): the study did not find a statistically significant difference between rehabilitation with RAGT when compared to physiotherapy assisted locomotion training [96].

Gehstrecke: Ø in 1 RCT

GD was reported by one study (chronic; n=48): the study did not find a statistically significant difference between rehabilitation with RAGT when compared to physiotherapy assisted locomotion training [96].

Balance: Ø in 3 RCTs

BAL was reported by three studies (subacute and chronic; n=174): none of the studies found a statistically significant difference in AtW when comparing RAGT to conventional physiotherapy or physiotherapy assisted locomotion training [95-97].

mobile Exoskelette: 2 RCTs

Mobile exoskeletons

For **mobile exoskeletons**, two RCTs compared the use of a double-leg exoskeleton [99] and a single-leg exoskeleton [14].

Double-leg exoskeleton

mobile Exoskelette (beidseitig) 1 RCT: keine stat. signifikanten Unterschiede in

For mobile exoskeletons, one study [99] compared a rehabilitation pathway incl. a HAL robot with weight relief to rehabilitation without HAL. Overall, there is low-quality evidence training with mobile exoskeleton and weight-bearing compared to conventional gait training results in no additional improvement in AtW, GD and BAL.

Gehfähigkeit, Gehgeschwindigkeit Gehstrecke und Balance

AtW was reported by the included study (subacute; n=28): no statistically significant difference was found between groups in FAC or SIS mobility score hereby [99].

WS was not reported by the included study [99].

GD was reported by the included study (subacute; n=28): no statistically significant difference was found between groups in 2 meters walk test [99].

BAL was reported by the included study (subacute; n=28): no statistically significant difference was found between groups in the berg balance scale [99].

Single-leg exoskeleton

mobile Exoskelette (einseitig): 1 RCT

For single-leg exoskeleton robots, one study [14] compared gait training with a bionic leg to group training without gait training. Overall, there is low-quality evidence that training with motorized knee single-joint orthosis compared with conventional gait training results in no additional improvement in AtW, WS, GD, and BAL

AtW was reported by the included study (chronic; n=20): the study did not find a statistically significant difference between rehabilitation with a single-leg exoskeleton and a conventional rehabilitation pathway [14].

Gehfähigkeit: Ø

WS was reported by the included study (chronic; n=20): the study did not find a statistically significant difference between rehabilitation with a single-leg exoskeleton and a conventional rehabilitation pathway [14].

Gehgeschwindigkeit: Ø

GD was reported by the included study (chronic; n=20): the study did not find a statistically significant difference between rehabilitation with a single-leg exoskeleton and a conventional rehabilitation pathway [14].

Gehstrecke: Ø

BAL was reported by the included study (chronic; n=20): the study did not find a statistically significant difference between rehabilitation with a single-leg exoskeleton and a conventional rehabilitation pathway [14].

Balance: Ø

Stationary End-Effectors

Five studies [100-104] investigated the use of **stationary end-effector** gait trainers. Overall, there is moderate quality evidence that end-effector-assisted training combined with conventional gait training additionally improves AtW in stroke patients who are unable to walk independently in the (early) subacute stadium. Further, conflicting evidence was found, whether end-effector assisted training combined with conventional training is superior to conventional training alone with regard to WS in this phase after stroke. Very low quality evidence was found that there is no additional improvement in GD and BAL. Additionally, there is low level evidence, that end-effector assisted gait training in combination with conventional gait training is not superior to conventional gait training alone regarding AtW and BAL in patients with chronic stroke. There is conflicting evidence whether end-effector assisted gait training is superior to conventional gait training or not in terms of WS and GD in chronic stroke.

stationäre End-Effektoren: 5 RCTs

AtW was reported in four studies (subacute and chronic; n=331): While two studies [102, 103] found a significant between group difference favouring end-effector based gait training in the subacute stadium, the remaining studies [101, 104] did not find a significant difference between end-effector assisted gait training and conventional gait training.

Gehfähigkeit:
+ in 2 RCTs
Ø in 2 RCTs

WS was reported in five studies (subacute and chronic; n=361): While two studies [100, 103] found a statistically significant between group difference favouring end-effector assisted gait training, the remaining three studies [101, 102, 104] failed to show a statistically significant[19] between group difference.

Gehgeschwindigkeit:
+ in 2 RCTs
Ø or n.g. in 3 RCTs

GD was reported by four studies (subacute and chronic; n=331): Only one [100] out of these studies [100-102, 104] found a statistically significant between group difference favouring end-effector based gait training hereby.

Gehstrecke:
+ in 1 RCT
Ø or n.g. in 3 RCTs

BAL was reported in two studies (subacute and chronic; n=146): Both studies [101, 104] failed to show a statistically significant between group difference favouring end-effector based gait training.

Balance:
Ø in 2 RCTs

[19] One study was not considered by the AWMF working group, due to the severity of the clinical deficit, baseline and early measurements of walking speed and gait distance could only be obtained during assisted walking in non-ambulatory patients.

Health-related quality of life

Health-related quality of life was not reported by the included studies[20].

Patient satisfaction

Patient satisfaction was not reported in the included studies [21].

Patient safety

Sicherheit in 4 Studien berichtet

Overall, four out of eleven studies reported on safety outcomes with regard to RAR.

keine UEs oder SUEs

For **stationary exoskeletons**, only one out of four includes studies [95-98] reported on safety outcomes: the RCT [98] reported that no SAEs occurred in 37 patients, of which 20 received RAGT with stationary exoskeletons. No further information were provided with regard to AEs.

For **mobile exoskeletons,** one included RCTs did not report on safety endpoints for double leg exoskeletons [99]. For single-leg exoskeletons, one RCT [14] reported on safety endpoints: no AEs occurred hereby.

For **stationary end-effectors**, two [100, 104] out of five studies [100-104] reported on safety endpoints: no AEs occurred hereby.

[20] D0012 – What is the effect of lower limb RAR on generic health-related quality of life?
D0013 – What is the effect of lower limb RAR on disease-specific quality of life?

[21] D0017 – Was the use of lower limb RAR worthwhile?

Table 3-1: Summary table of results of primary outcomes of randomised controlled trials (LoE: 1b only) on robotics for stroke rehabilitation

LoE	Autor/ year	Intervention	Length of FU	N of pts (IG/CG)	Stadium; severity; setting	Ability to walk (AtW)	Walking speed (WS)	Gait distance (GD)	Balance (BAL)	AE	Conclusion (GRADE)
Stationary Exoskeletons											
1b +	Chang et al. 2012 [98]	■ RAGT (Lokomat) vs. ■ conventional gait training	PI (2 w.)	37 (20/17)	Subacute; FAC<2; inpatient	Ø				No SAEs occurred AEs: NR	At present, there is moderate quality evidence that RAGT may not additionally improve AtW and Balance. Low quality evidence suggests that it may not additionally improve WS and GS
1b +	Han et al. 2016 [97]	■ RAGT (Lokomat) vs. ■ conventional gait training on the floor	PI (4 w.)	60 (30/30)	Subacute; FAC<2; inpatient	Ø			Ø	NR	
1b +	Mayr et al. 2019 [95]	■ RAGT (Lokomat) vs. ■ conventional gait training on the floor	PI (8 w.)	66 (36/30)	Subacute; FAC between 1 and 2; inpatient	Ø			Ø	NR	
1b +	Hornby et al., 2008 [96]	■ RAGT (Lokomat) vs ■ physiotherapy-assisted lokomotion training	6 m.	48 (24/24)	Chronic; able to walk >10 m. without assistance; inpatient		Ø	Ø	Ø	NR	
Mobile Exoskeletons											
Double-leg exoskeleton											
1b +	Wall et al., 2019 [99]	■ Rehabilitation incl. HAL with weight relief vs. ■ Rehabilitation without HAL	6 m.	15/13	Subacute; inability to walk or in need of continuous manual support to walk; inpatient	Ø (FAC; SIS mobility)		Ø (2MWT)	Ø (BBS)	NR	Low-quality evidence that training with mobile exoskeleton and weight-bearing compared with conventional gait training results in no additional improvement in AtW, GD and BAL
Single-leg exoskeletons											
1b +	Stein et al., 2014 [14]	■ Gait training with bionic leg vs. ■ Group training without gait training	3 m.	10/10	Chronic, able to walk; independent in household ambulation (with or without the use of a unilateral assistive device); outpatient	Ø (EFAP)	Ø (10 m)	Ø (6 min)	Ø (TUG, 5TSTS BBS)	None occurred	Low-quality evidence that training with motorized knee single-joint orthosis compared with conventional gait training results in no additional improvement in AtW, WS, GD and BAL

LoE	Autor/ year	Intervention	Length of FU	N of pts (IG/CG)	Stadium; severity; setting	Ability to walk (AtW)	Walking speed (WS)	Gait distance (GD)	Balance (BAL)	AE	Conclusion (GRADE)
Stationary End-Effectors											
1b +	Geroin et al., 2011 [100]	■ Gait training with GT and DC stimulation ■ Gait training with GT and sham stimulation ■ Conventional overground training	PI (2 w.)	10/10/10 (2 vs. 3)	Chronic, able to walk independently for at least 15 m with the use of walking aids; outpatient		+	+		None occurred	At present there is low level evidence, that end-effector assisted gait training in combination with conventional gait training is not superior to conventional gait training alone regarding AtW and BAL in patients with chronic stroke. There is, conflicting evidence whether end-effector assisted gait training is superior to conventional gait training or not in terms of WS and GD in chronic stroke.
1b +	Dias et al., 2007 [101]	■ Gait training with GT1 + conventional training (40 Min) ■ Group training with conventional gait training (40 Min)	3 m.	20/20	Chronic, stabilised motor deficits; NR	Ø	Ø	Ø	Ø	NR	
1b +	Pohl et al., 2007 [102]	■ Conventional gait training and gait trainer GT1 vs. ■ Conventional gait training without gait trainer	6 m.	77/78	Subacute; NR; outpatient	+	n.g.	n.g.		NR	There is moderate quality evidence that end-effector-assisted training combined with conventional gait training additionally improves **AtW** in stroke patients who are unable to walk independently in the (early) subacute stadium. There is conflicting evidence, whether end-effector assisted training combined with conventional training is superior to conventional training alone with regard to WS in this phase.after stroke. There is very low quality evidence that there is no additional improvement in **GD** and **BAL**.
1b +	Hesse et al., 2012 [103]	■ Conventional gait training with gait trainer vs ■ Conventional gait training without gait trainer	3 m.	15/15	Subacute; Wheelchair-mobilized and partially independent in basic activities of living; inpatient	+	+			NR	
1b +	Chua et al. 2016 [104]	■ Conventional gait training with gait trainer ■ Conventional gait training without gait trainer	12 m.	53/53	Subacute; NR; inpatient	Ø	Ø	Ø	Ø	None occurred	

Notes: Only results for selected primary outcomes are depicted in this table. Further detailed information can be found in the AWMF S2 guideline to be published soon.

Explanations: *+/- significant effects for/against the additional intervention, Ø no significant group differences; ND = no statistical data available (for group comparison)*

Abbreviations: *AE – adverse event(s); AtW – ability to walk; BAL – balance; FAC – functional ambulation category; FES – functional electrical stimulation; FU – follow up; GD – gait distance; GRADE – Grading of Recommendations, Assessment, Development and Evaluation; LoE – level of evidence; m. – month(s); N – number; NR – not reported; PI – post-intervention; RAGT – robot assisted gait training; w.- weeks; WS – walking speed.*

3.3 Effectiveness and safety of functional electrical stimulation for lower limb stroke rehabiliation

3.3.1 Included studies

Study characteristics

17 RCTs

In this assessment, we found six new RCTs to be included in addition the eleven RCTs already included in the initial guideline published in 2015 [37]. Hence, the body of evidence consists of 17 RCTs evaluating the clinical benefit of FES for lower limb stroke rehabilitation.

nur 1b Lo

The LoE of the individual studies was judged to be 1b for all included individual studies (++ for 2 RCTs and + for the remaining RCTs).

7 Subinterventionen; FES

The interventions in the included studies differed with respect to the specific modality of FES:

- *FES with surface electrodes during walking:* two studies focused on nervus peroneus FES (chronic; n=142) [105-107] and multi-channel FES (subacute and chronic; n=53) [108, 109] respectively. Gait training with flexor reflex stimulation was evaluated in one study (subacute; n=30) [110]. There we0re some further two studies (chronic; n=692) focusing on tilt sensor FES [111-113].
- *Electrostimulation of the peroneal nerve while walking:* one study [114] used an implanted system (chronic; n=25).
- *Multi-channel FES with percutaneous wire electrodes:* one study [115] used this FES modality (chronic; n=32).
- *FES in combination with electromechanical gait trainer*: two further studies (subacute; n=104) evaluated the use of this FES modality [116, 117].
- *Mixed electrostimulation programs (also while walking)*: one study (subacute; n=38) was found for mixed electrostimulation programs (also while walking) [118].
- *Bike training (cycling) with FES*: four studies (subacute and chronic; n=168) evaluated the use of [119-122].
- *Treadmill training with FES*: one study evaluated the use of FES in combination to treadmill training [123].

mit Oberflächenelektroden 7 RCT

des N. Peroneus (implantiert): 1 RCT

mit perkutanen Drahtelektroden (Mehrkanal): 1 RCT

mit elektromech. Gangtrainer: 2 RCT

(gemischte Programme): 1 RCT

und Fahrradtraining: 4 RCT

und Laufbandtraining: 1 RCT

The length of follow-up in the included studies ranged from 4 weeks to one year.

Patient characteristics, stroke stadium and setting

Unterschiede in Stadium des Schlaganfalls und

Nine studies [108, 110, 116-122] enrolled patients in the subacute stadium and further eight studies [105-107, 109, 111-115, 123] enrolled chronic stroke patients.

Grad der Beeinträchtigung

The severity/level of impairment was reported in 14 out of 17 studies: six studies enrolled patients that were able to walk 10 meters [105-107, 110-113] or 15 meters [123]. One study stated that the enrolled patients needed to be able to walk at least 15 minutes for 4 times a week [109] and another study stated solely that the patients were able to walk unassisted at time of enrolment [115]. Three studies stated that the FAC score needed to be less than 3 [116, 117, 119]. Another study enrolled patients that were not able to walk 50 meters [122]. Two further studies reported the level of impairment less precisely, with stating that the patients were not able to walk [118] or had severe hemiplegia [108].

Setting berichtet in 13 Studien: stationär: 8 RCT ambulant: 4 RCT 1 RCT in Reha-Klinik (ohne eindeutige Beschreibung)

The setting was reported in 13 out of 17 studies: eight studies [108, 111, 116, 117, 119-121, 123] enrolled patients in the inpatient setting and further four studies/six publications [105, 106, 109, 112-114] evaluated FES in the outpatient setting. One further study [110] used FES in a rehabilitation clinic, without clearly stating whether outpatients or inpatients were enrolled hereby.

A brief description of the included studies and results are displayed in the summary table of the evidence (Table 3-2). Study characteristics and results of new eligible studies from the update search can be found in Table A-1.

3.3.2 Results

Function[22]

Functional electrostimulation (FES) with surface electrodes during walking

N. Peroneus FES: 2 RCT

For **N. peroneus FES**, two studies/three publications were included [105-107]: the studies compared rehabilitation with a stimulator of the Nervus peroneus to standard rehabilitation. Overall, moderate-quality evidence was found indicating that rehabilitation with N. peroneus FES is not superior to standard rehabilitation in terms of the endpoints AtW (1 RCT, chronic; n=110) and WS (2 RCTs; chronic; n=142).

Gehfähigkeit: Ø in 1 RCT

AtW was reported in one study [105, 106], enrolling 110 subacute post-stroke patients: no statistically significant difference was found between rehabilitation with FES and standard rehabilitation alone.

Gehgeschwindigkeit: Ø in 2 RCT

WS was reported in both studies (n=142; chronic), with none of these studies finding a statistically significant difference hereby [105-107].

The endpoints *GD* and *BAL* were not reported in any of the included studies [105-107].

Gangtraining mit schrittsynch. Stimulation von Flexorreflex-Afferenzen: 1 RCT

For **gait training with flexor reflex stimulation**, one study [110], comparing intensive physiotherapy based gait training with flexor reflex stimulation to intensive physiotherapy based gait training alone, was included. Low-quality inconclusive evidence was found indicating that gait training with flexor reflex stimulation improves WS (1 RCT; subacute; n=30). Inconclusive low-quality evidence was found for AtW (1 RCT; subacute; n=30).

Gehfähigkeit: Ø in 1 RCT

For the endpoint *AtW*, the study (n=30) did not find a statistically significant difference between subacute stroke patients undergoing gait training with flexor reflex stimulation in comparison to gait training without stimulation [110].

Gehgeschwindigkeit: + in 1 RCT

WS was reported by the included study [110]: the RCT (n=30) found a statistically significant difference favouring gait training with flexor reflex stimulation in subacute stroke patients.

The endpoints *GD* and *BAL* were not reported by the included study [110].

[22] D0011 – What is the effect of FES on patients' body functions?, D0016 – How does the use of FES affect activities of daily living?

For **multi-channel FES,** two studies [108, 109], comparing gait training with assistive multi-channel FES to gait training without FES, were included. inconclusive low-quality evidence was found indicating that gait training with this subtype of FES is superior to standard rehabilitation alone in terms of WS (2 RCTs; subacute and chronic; n=53) and GD (1 RCT; chronic; n=33).

FES mit Mehrkanal-Systemen: 2 RCT

The endpoint AtW was not reported in any of the studies [108, 109].

The endpoint *WS* was reported by both studies [108, 109]: one study [108] enrolling 20 subacute stroke patients found a statistically significant difference favouring rehabilitation with multi-channel FES in comparison to standard rehabilitation alone (however, only for differences to the baseline measurement and not for absolute values) and the other study [109] enrolling 33 patients did not find a statistically significant group difference.

Gehgeschwindigkeit: + in 1 RCT Ø in 1 RCT

The endpoint *GD* was reported by one study [109]: a statistically significant difference was found when comparing everyday use of a 2 channel FES system and gait training with FES to gait training without FES in 18 and 15 patients respectively.

Gehstrecke: + in 1 RCT

The endpoint BAL was not reported in the included RCTs [108, 109].

For **tilt sensor FES**, two studies/three publications were included that compared standard rehabilitation with tilt sensor FES (in the form of a drop foot stimulator) to standard rehabilitation (incl. AFO) alone [111-113]. Overall high-quality evidence (2 RCTs; chronic; n=692) was found that tilt sensor FES may not be superior but non-inferior to AFO in terms of AtW, WS and GD. The evidence was less robust (moderate) for BAL.

Neigungssensor FES: 2 RCT

The endpoint *AtW* was reported by both studies (2 RCTs; chronic; n=692): none of the studies found a statistically significant difference between different modes of tilt sensor FES and AFO [111-113].

Gehfähigkeit: Ø in 2 RCT

WS was reported by both studies (2 RCTs; chronic; n=692): none of the studies found a statistically significant difference between different modes of tilt sensor FES and AFO [111-113]. One study specifically tested for non-inferiority of this outcome and found FES to be statistically significantly non-inferior to AFO [112, 113] hereby.

Gehgeschwindigkeit: Ø in 2 RCT stat. signifikant nicht-unterlegen in 1 RCT

The endpoint *GD was* reported by two studies (2 RCTs; chronic; n=692): none of the studies found a statistically significant difference between different modes of tilt sensor FES and AFO [111-113].

Gehstrecke: Ø in 2 RCT

BAL was reported by both studies (2 RCTs; chronic; n=692): one study [112, 113] did not find a statistically significant difference in BAL when comparing FES drop foot systems to standard rehabilitation including AFO. The other study [111] found mixed results within the endpoint BAL: while no statistically significant difference was found in the TUG score between groups, a statistically significant difference in the BBS score was found to the detriment of a FES drop foot system [111-113].

Balance: Ø in 1 RCT; - in 1 RCT

Electrostimulation of the peroneal nerve while walking with implanted System

For electrostimulation of the peroneal nerve (also while walking) with an implanted system, one study was included [114]. Low-quality inconclusive evidence was found indicating that gait training with **implanted N. peroneus FES** is not superior to standard rehabilitation in terms of WS (1 RCT; chronic; n=25).

Elektrostimulation des N. Peroneus während des Gehens mit implantiertem System: 1 RCT

The endpoint *AtW* was not reported by the RCT [114].

Gehgeschwindigkeit: Ø in 1 RCT

WS was reported by the RCT (chronic; n=25): the study [114] found no statistically significant differences between a 2-channel stimulator for step-synchronous stimulation of the N. peroneus in comparison to a use of the preferred conventional orthosis.

GD and *BAL* were not reported by the RCT [114].

Multi-channel FES with percutaneous wire electrodes

Mehrkanal-FES mit perkutanen Drahtelektroden: 1 RCT

For multi-channel FES with percutaneous wire electrodes, one study that compared this FES modality combined to standard rehabilitation to standard rehabilitation alone was included [115]. Low-quality inconclusive evidence was found indicating that gait training with **multi-channel FES with percutaneous wire electrodes** is not superior to standard rehabilitation in terms of GD (1 RCT, chronic; n=32).

Gehfähigkeit: kein Gruppenvergleich

The endpoint *AtW* was reported by the RCT (chronic; n=32), but there was no data on the statistical group difference available [115].

WS was not reported by the RCT [115].

Gehstrecke: Ø in 1 RCT

GD was reported by the RCT (chronic; n=32): no statistically significant difference (in favour of FES) was observed when comparing FES with intramuscular percutaneous electrodes during a 12 week training to the 12 week training alone [115].

BAL was not reported by the RCT [115].

FES combined with electromechanical gait trainer

FES kombiniert mit elektromechanischem Gangtrainer: 2 RCT

Two studies [116, 117] were included that compared FES combined with electromechanical gait trainer to conventional gait training plus physiotherapy. Very-low quality inconclusive evidence (2 RCTs; subacute; n=72[23]) was found indicating that **FES combined with electromechanical gait trainer** improves AtW and WS when compared to standard rehabilitation alone and does not improve AtW and WS when compared to electromechanical gait training without FES. For the endpoint BAL, very-low quality inconclusive evidence was found showing no statistically significant difference in both trials regardless of the comparator. [24]

Gehfähigkeit: + in 2 RCT

AtW was reported in both RCTs (2 RCTs; subacute; n=72[23]): While both studies found a statistically significant difference favouring FES in combination with electromechanical gait training in comparison to conventional rehabilitation, this difference was not significant when compared to electromechanical gait training without FES [116, 117].

Gehgeschwindigkeit: + in 2 RCT

WS was reported in both trials (2 RCTs; subacute; n=72[23]): While both studies found a statistically significant difference favouring FES in combination of electromechanical gait training in comparison to conventional rehabilitation, this difference was not significant when compared to electromechanical gait training without FES.

GD was not reported by the RCTs [116, 117].

---

[23] Excluding the group receiving electromechanical gait trainer without FES.

[24] The initial guideline considered these publications to be two independent RCTs. It is to be noted that both "RCTs" declare their publications as individual RCTs, however, double publication was suspected by the guideline due to substantial similarities between both studies.

BAL was reported by both trials (2 RCTs; subacute; n=72[23]): none of these studies found a statistically significant difference regardless of the comparator (conventional rehabilitation, electromechanical gait trainer without FES) [116, 117].

Balance:
Ø in 2 RCT

Mixed electrostimulation programs lower extremity (also while walking)

One study [118] was included comparing cyclical electrostimulation of the peroneal nerve and functional training (incl. manually triggered FES) to supervised self-exercise and functional training without FES. Very-low quality inconclusive evidence was found indicating that **mixed electrostimulation programs lower extremity (also while walking)** improves AtW when used additionally to standard rehabilitation (1 RCT; subacute; n=38).

gemischte Elektrostimulations-Programme (auch während des Gehens):
1 RCT

AtW was reported by the RCT [118]: a statistically significant difference was observed, but group differences were only reported for the differences to the baseline measurement, not for absolute values.

Gehfähigkeit:
+

The endpoints *WS*, *GD* and *BAL* were not reported by the RCT [118].

Bike training (Cycling) with FES

Four studies [119-122] were included that compared bike training with FES to bike training without FES or placebo FES. Inconclusive very low-quality evidence was found indicating that **bike training with FES** is superior to bike training alone in terms of AtW (2 RCTs; subacute; n=80) and WS (3 RCTs; subacute and chronic; n=90).

Fahrradtraining (Cycling) mit FES:
4 RCT

The endpoint *AtW* was reported in two RCTs (subacute; n=80): one study [120] with 40 enrolled patients found no statistically significant difference between FES cycling and cycling without FES. Another study [119] also with 40 enrolled patients found a statistically significant difference in AtW favouring FES cycling at post-intervention. Two weeks after treatment, however, this difference was not statistically significant anymore.

Gehfähigkeit:
Ø in 1 RCT
+ in 1 RCT

WS was reported in three RCTs (subacute and chronic; n=90): While two studies [121, 122] with 20 and 30 enrolled patients respectively did not find a statistically significant difference, one study [119] with 40 patients found a statistically significant difference at post-intervention favouring FES cycling. However, the study did not report whether this difference was also statistically significant at follow-up.

Gehgeschwindigkeit:
Ø in 2 RCT
+ in 1 RCT

The endpoints *GD* and *BAL* were not reported by any of the RCTs [119-122].

Treadmill training with FES

One study [123] was included that compared treadmill training with FES to treadmill training with sham FES. Overall, low-quality inconclusive evidence indicates that FES with treadmill training improves WS and BAL in comparison to treadmill training alone (1 RCT; chronic; n=32).

Laufbandtraining mit FES:
1 RCT

AtW was not reported by the included study [123].

WS was reported by the RCT (chronic; n=32): the study found a statistically significant difference in WS favouring treadmill training with FES when compared to treadmill training without FES [123].

Gehgeschwindigkeit:
+ in 1 RCT

GD was not reported by the included study [123].

BAL was reported by the RCT (chronic; n=32): the study found a statistically significant difference in BAL favouring treadmill training with FES when compared to treadmill training without FES [123].

Balance:
+ in 1 RCT

Health-related quality of life[25]

Lebensqualität in 2 Studien berichtet: Ø

stat. signifikant nicht-unterlegen in 1 RCT

Stroke specific QoL was reported in two out of 17 RCTs [105, 106, 112, 113]: no significant difference was found in one study [112, 113] that enrolled 495 patients and compared the Walkaide® FES system to AFO and another study [105, 106] that enrolled 110 patients and compared the peroneal nerve stimulation (Odstock Medical Inc.) to standard rehabilitation. The former study [112, 113] further conducted a statistical test for non-inferiority and found that the SIS scale (including quality of life domains) was statistically non-inferior hereby.

Patient satisfaction[26]

Patient*innen-zufriedenheit in 2 RCT: Therapieabbruch in 1 RCT: 2.9 % vs. 4 % Benutzerzufriedenheit in 1 RCT: +

Patient satisfaction with the study device was reported in two out of 17 included RCTs: one study [112] with 495 patients found that 7 (2.9%) and 10 (4%) in the FES and AFO group respectively discontinued the therapy because of dissatisfaction. Another study [111] stated that user satisfaction was statistically significantly different favouring FES in comparison to AFO. However, the study did not report on the instrument used to measure satisfaction.

Patient safety[27]

Sicherheit in 5 Studien berichtet

Overall, five studies (six publications) reported on safety outcomes with regard to FES devices [111-113, 116, 117, 119].

Neigungssensor FES: 1 RCT: 242 Pts mit WalkAide® FES vs. 253 Pts mit AFO 422 vs. 437 Komplikationen SAEs: 2,9 % vs. 1,9 %

stat. signifikant nicht-unterlegen Stürze: 20,2 % vs. 20,4 % "andere" AEs: 20,2 % vs. 22 % vs. 27,4 % Hautreizung: 3,9 % vs. 1,2 % Muskelschmerz: 1,75 % vs. 1.75 %

The safety of **tilt sensor FES** was reported in two studies: one study [112, 113] compared the WalkAide® FES system in combination to standard rehabilitation in 242 chronic stroke patients as compared to conventional AFO and standard rehabilitation in 253 chronic stroke patients and found 0 (0%) and 2 (0.2%) SAEs that were related to the study devices respectively. Overall, 422 and 437 complications occurred. Some 25 (2.9%) and 16 (1.9%) of the patients experienced SAEs in the FES and AFO group respectively. The study further tested the differences for non-inferiority and found the WalkAide® FES system to be statistically significantly non-inferior to AFO ($p<0.001$). Further AEs were reported by the study: falls were reported in 173 patients (20.2%) in the WalkAide® FES group as opposed to 175 patients (20.4%) in the AFO group. Other AEs (e.g., fatigue or muscle weakness or other medical conditions) accumulated to occur in 189 patients (22%) in the WalkAide® FES group in comparison to 235 patients (27.4%) in the AFO group. Skin irritation and muscle soreness occurred less frequently: 34 patients (3.9%) versus 10 patients (1.2%) developed skin irritation and 15 patients (1.75%) versus 15 patients (1.75%) had muscle soreness in the WalkAide® FES and AFO group respectively.

---

[25] D0012 – What is the effect of FES assisted lower limb stroke rehabilitation on generic health-related quality of life?,
D0013 – What is the effect of FES assisted lower limb stroke rehabilitation on disease-specific quality of life?

[26] D0017 – Was the use of FES assisted lower limb stroke rehabilitation worthwhile?

[27] C0008 – How safe is FES assisted lower limb stroke rehabilitation in comparison to standard rehabilitation alone?

The safety of the foot drop system (NESS L300) was evaluated and compared to an AFO in another study [111] (chronic; n=197): SAEs occurred in some 14 and six patients in the FES group and standard rehabilitation (incl. AFO) group respectively. However, none of these were related to the rehabilitation device. Further, statistically significantly more AEs occurred in the FES group in comparison to the AFO group, with some 219 and 147 AEs occurring in these groups respectively. There were statistically significantly more device related AEs: 130 and 50 device related AEs occurred in FES and AFO group respectively.

1 RCT: 99 Pts mit NESS L300 vs. 98 mit AFO
SAEs: 14 vs. 6 (nicht in Zusammenhang mit FES);
AEs: 219 vs. 147;
AEs in Zusammenhang mit FES: 130 vs. 50
(stat. signifikant)

The safety of **FES combined with electromechanical gait training** was further evaluated in two RCTs (2 RCTs; subacute; n=72), stating that no AEs occurred from the training [116, 117].

FES mit elektromechanischem Gangtrainer:
keine AEs in 1 Studie

Further, the safety of **bike training (cycling) with FES** was evaluated in one study (subcacute; n=40): no SAEs or AEs occurred in the active cycling with FES group when compared to the active cycling without FES group [119].

Fahrradtraining mit FES:
keine AEs/SAEs in 1 Studie

Table 3-2: Summary table of results of primary outcomes of randomised controlled trials (LoE: 1b only) on functional electrical stimulation (FES) for stroke rehabilitation

LoE	Autor/ year	Intervention	Length of FU	N of pts (IG/CG)	Stadium; severity; setting	Ability to walk (AtW)	Walking speed (WS)	Gait distance (GD)	Balance (BAL)	AE	Conclusion (GRADE)
FES with surface electrodes during walking											
N. peroneus FES											
1b, +	Burridge et al. 1997 [107]	■ Care with stimulator of the nervus peroneus (ODFS) plus physiotherapy for 1 m. vs. ■ physiotherapy only for 1 m.	3 m.	32 (16/16)	Chronic; able to walk 10m.; NR		Ø			NR	At present, moderate-quality evidence indicating that **N. peroneus FES** is not superior to standard rehabilitation in terms of AtW and WS
1b, +	Sheffler et al 2013/2015 [105, 106]	■ Peroneal nerve stimulation (ODFS) and stan dard rehabilitation for 3m. vs. ■ Standard rehabilitation (incl. AFO in 48/56 pts) for 3 m.	9 m.	110 (54/56)	Chronic; able to walk 10m. unassisted; outpatient	Ø	Ø			NR	
Gait training with flexor reflex stimulation											
1b, +	Spaich et al. 2014 [110]	■ Intensive physiotherapy-based gait training with flexor reflex stimulation[28] for 1m. vs. ■ Intensive physiotherapy-based gait training without stimulation for 1m.	NR	30 (15/15)	Subacute; able to walk 10m.; rehabilitation clinic	Ø (FAC)	+			NR	At present, there is inconclusive low-quality evidence that gait training with **flexor reflex stimulation** improves WS Inconclusive low-quality evidence was found for AtW
Multi-channel FES											
1b, + Crossover RCT	Bogataj et al. 1995 [108]	■ Gait training with 5-6 channel FES[28] plus conventional therapy for 6w. vs. ■ Conventional therapy including gait training without stimulation for 6w.	NR	20 (10/10)	Subacute; severe hemiplegia; inpatient		(+)[29]			NR	At present, inconclusive low-quality evidence that gait training with **multi-channel FES** is superior to standard rehabilitation alone in terms of WS and GD
1b, +	Embrey et al. 2010 [109]	■ Everyday use of a 2-channel FES system (Gait MyoElectric Stimulator; plantar/dorsiflexion reflectors) plus gait training with FES for 3 m. vs. ■ Gait training without FES for 3 m.	NR	33 (18/15)	Chronic; able to walk 15m. for at least four times a day; outpatient		Ø	+		NR	

[28] FES device product name not reported.

[29] Significant group differences only for the differences to the baseline measurement, not for absolute values.

LoE	Autor/ year	Intervention	Length of FU	N of pts (IG/CG)	Stadium; severity; setting	Ability to walk (AtW)	Walking speed (WS)	Gait distance (GD)	Balance (BAL)	AE	Conclusion (GRADE)
Tilt sensor FES											
1b, ++	Bethoux et al. 2014/2015 [112, 113]	■ WalkAide® FES and standard rehabilitation for 6 m. vs. ■ Conventional AFO and standard rehabilitation for 6 m.	6 m. (incl. 12 m. post-hoc analysis)	495 (242/253)	Chronic; able to walk 10 m.; outpatient	Ø	Ø	Ø	Ø	422 vs. 436 Ø and s. s. non-inferior to AFO AEs included, inter alia, falls, skin irritation, muscle soreness	At present, high-quality evidence that **tilt sensor FES** is not superior but non-inferior to AFO in terms of AtW, WS and GD. The evidence was less robust (moderate) for BAL.
1b, ++	Kluding et al. 2013 [111]	■ FES (NESS L300) and SoC for 30 w. vs. ■ Conventional AFO and SoC for 30 w.	30 w.	197 (99/98)	Chronic; able to walk more than 10 meters; inpatient	Ø	Ø	Ø	Ø (TUG) – (BBS)	SAE: ND (14 vs. 6) AE: – (219 vs. 147) AE related to device: – (130 vs. 50)	
Electrostimulation of the peroneal nerve while walking with implanted System											
1b, +	Kottink et al. 2008 [114]	■ Implantation of a 2-channel stimulator for step-synchronous stimulation[28] of the nervus peronaeus and use of the system for walking in everyday life for 6 months vs. ■ Further use of the preferred orthosis or walking without aids	26 w.	25 (13/12)	Chronic; NR; outpatient		Ø			NR	At present, inconclusive low-quality evidence indicating that gait taining with impanted **N. peroneus FES** is not superior to standard rehabilitation in terms of WS
Multi-channel FES with percutaneous wire electrodes											
1b, +	Daly et al. 2006 [115]	■ Functional electrical multi-channel stimulation with intramuscular percutaneous electrodes[28] during a 12 week training program vs. ■ training without FES	12 w. (PT)	32 (16/16)	Chronic; able to walk without human assistance; NR	ND		Ø		NR	At present, inconclusive low-quality evidence indicating that gait training with **multi-channel FES with percutaneous wire electrodes** is not superior to standard rehabilitation in terms of GD

LoE	Autor/ year	Intervention	Length of FU	N of pts (IG/CG)	Stadium; severity; setting	Ability to walk (AtW)	Walking speed (WS)	Gait distance (GD)	Balance (BAL)	AE	Conclusion (GRADE)
FES combined with electromechanical gait trainer											
1b, +	Tong et al. 2006 [117]	■ gait training with electromechanical gait trainer combined with FES[28] plus physiotherapy vs. ■ conventional gait training plus physiotherapy	4 w.	35 (15/20)	Subacute; FAC<3; inpatient	+	+		Ø	No AEs occurred from the training	At present, inconclusive very-low quality evidence indicating that **FES combined with electromechanical gait trainer** improves AtW and WS when compared to standard rehabilitation alone and does not improve AtW and WS when compared to electromechanical gait training without FES
		■ gait training with electromechanical gait trainer combined with FES[28] plus physiotherapy vs. ■ electromechanical gait trainer without FES plus physiotherapy		30 (15/15)		Ø	Ø		Ø	No AEs occurred from the training	
1b, +	Ng et al. 2008 [116]	■ gait training with electromechanical gait trainer combined with FES[28] plus physiotherapy vs. ■ conventional gait training plus physiotherapy	6 m.	37 (16/21)	Subacute; FAC<3; inpatient	+	+		Ø	No AEs occurred from the training	
		■ gait training with electromechanical gait trainer combined with FES[28] plus physiotherapy vs. ■ electromechanical gait trainer without FES plus physiotherapy		33 (16/17)		Ø	Ø		Ø	No AEs occurred from the training	
Mixed electrostimulation programs lower extremity (also while walking)											
1b, +	MacDonell et al. 1994 [118]	■ 5 x weekly cyclical electrostimulation of the peroneal nerve and 3 x weekly functional training with manually triggered FES for 4 weeks vs. ■ 5 x weekly supervised self-exercise program and 3 x weekly functional training without FES for 4 weeks	3 m.	38 (20/18)	Subacute; not able to walk; NR	(+)[30]				NR	At present, inconclusive very-low quality evidence that **mixed electrostimulation programs lower extremity (also while walking)** improves AtW

[30] Significant group differences only for the differences of the FAC to the baseline measurement, not for absolute values.

LoE	Autor/ year	Intervention	Length of FU	N of pts (IG/CG)	Stadium; severity; setting	Ability to walk (AtW)	Walking speed (WS)	Gait distance (GD)	Balance (BAL)	AE	Conclusion (GRADE)
Bike training (Cycling) with FES											
1b, +	Ferrante et al. 2008 [121]	■ One session/d with 2 x 10 min FES induced and 3 x 5 min passive Cycling on a motor-assisted bicycle ergometer + standard rehabilitation 3 h/d for 4 weeks vs. ■ Standard rehabilitation without FES (same scope of therapy) for 4 weeks	4 w.	20 (10/10)	Subacute; NR; inpatient		Ø			NR	At present, inconclusive very low-quality evidence that **bike training with FES** is superior to bike training alone in terms of AtW and WS
1b, +	Ambrosini et al. 2011 [122]	■ FES supported (15min) and passive (2 x 5 min) cycling on a motor-assisted bicycle ergometer 5 x weekly + standard rehabilitation vs. ■ Same therapy, but with placebo stimulation	3-5 m.	30 (15/15; Stroke: 14/13, TBI: 1/2)	Subacute; not able to walk 50 meters; NR		Ø			NR	
1b, +	Bauer et al. 2015 [119]	■ Active leg cycling with FES for 4 w. vs. ■ Active leg cycling without FES for 4 w.	6 w.	40 (21/19)	Subacute; inpatient; FAC 2 or lower; inpatient	+ (FAC, POMA, PI) Ø (FAC, POMA, FU)	+ (10MWT, PI)			SAE: 0 (0) vs. 0 (0) AE: 0 (0) vs. 0 (0)	
1b, +	De Sousa et al. 2016 [120]	■ FES Cycling for 4 w. and standard rehabilitation vs. ■ standard rehabilitation alone for 4 w.	4 w.	40 (20/20)	Subacute; NR; inpatient	Ø				NR	
Treadmill training with FES											
1b, +	Hwang et al. 2015 [123]	■ Treadmill training with tilt sensor FES (WalkAide® System) for 4 w. vs. ■ Treadmill training with sham FES for 4 w.	4 w.	32 (16/16)	Chronic; able to walk more than 15 meters; inpatient		+		+	NR	At present, inconclusive low quality evidence that **treadmill training with FES** improves WS and BAL in comparison to treadmill training alone.

Notes: Only results for selected primary outcomes are depicted in this table. For secondary outcomes such as quality of life, results of studies identified by the update search can be found in Table A-1. None of the studies identified by the initial guideline reported on quality of life or patient satisfaction.

Explanations: +/- significant effects for/against the additional intervention, Ø no significant group differences; ND = no statistical data available (for group comparison)

Abbreviations: AE – adverse event(s); AtW – ability to walk; BAL – balance; FAC – functional ambulation category; FES – functional electrical stimulation; FU – follow up; GD – gait distance; GRADE – Grading of Recommendations, Assessment, Development and Evaluation; LoE – level of evidence; m. – month(s); N – number; NR – not reported; ODFS – Oddstock Dropped Foot Stimulator; PI – post-intervention; POMA – Performance Oriented Mobility Assessment; SAE – serious adverse event(s); SoC – standard of care; w.- weeks; w.- weeks; WS – walking speed.

4 Upper limb stroke rehabilitation

4.1 Outcomes

Outcomes to evaluate the effectiveness and safety of upper limb stroke rehabilitation are based on the AWMF S3 guideline [4] and are briefly described in this section. Due to the large number of scientific instruments used in the studies included into the guideline [1], the reader is reminded that the outcome instruments listed in this section are not exhaustive.

4.1.1 Clinical effectiveness

wesentlicher Zielparameter: Aktivitäten des Alltags

weitere Endpunkte: Körperfunktionalität, Einschränkungen der Aktivität, Muskelkraft, Patient*innenzufriedenheit und Lebensqualität

Aktivitäten des Alltags: verschiedene Tools: z. B. FIM, BI, MAL

The following outcome was selected as crucial:

- Activities of daily living (ADL)

The following outcomes were defined as relevant:

- Body function and structure (BF)
- Activity limitations (AL)
- Muscle strength (MS)
- Patient satisfaction (PSA) with the device
- Health-related Quality of Life (HRQoL)

Activities of daily living (ADL) is a crucial outcome to evaluate the effectiveness of upper limb stroke rehabilitation, being defined as "daily household-based activities that people carry out to maintain health and well-being" such as eating, dressing and drinking [124]. There are several instruments assessing ADL. These can be assessed, for instance, by using the following instruments:

- *Functional Independence Measure (FIM):* FIM is a 18-items tool that evaluates the degree of impairment exploring how much caregiving the individual requires for completing ADL (e.g., eating, memory) which can be broken down into 13 motor tasks and five cognitive tasks. These are evaluated on a seven point ordinal scale ranging from total assistance to full independence with 18 being the lowest and 126 the highest possible score [125]. The score is measured twice, at admission and discharge of rehabilitation, where the resulting difference represents the change/gain in FIM [126].
- *Barthel Index (BI):* Similar to the FIM, the BI is used for evaluating the amount of assistance needed by a patient on ten activities of mobility and self-care (e.g., feeding, personal toileting and bathing). It combines a patient-reported outcome measure and a direct observation by the therapists on a 100 point scale. A higher value indicates a better level of independence after hospital discharge. Different versions of the BI exist like the extended BI (EBI), a 15-item version, which was also used as an instrument in one RCTs included in the guideline.
- *Motor Activity Log (MAL):* The Motor Activity Log being categorized as a semi-structured patient reported outcome measure for evaluating the arm function on the quality of movement (MAL-QOM) and Amount

of Movement (AOM) on either 30 daily functional activities, 28 functional activities or 14 activities makes use of a six point scale, where a higher score indicates a greater functional ability [127].

- *Chedoke McMaster Stroke Assessment (CMSA):* CMSA provides a measurement tool for physical impairment and activity of post-stroke patients. It is composed of two inventories: impairment inventory evaluating six dimensions (shoulder pain, recovery stage of postural control, arm, hand, leg, and foot) and the activity inventory rating assessing the gross motor function and walking ability. Each inventory is scaled on a seven point score ranging from one (full dependence) to seven (independent) [128].
- *Chedoke Arm and Hand Activity Inventory (CAHAI):* This outcome measure explores the ability of the paretic arm and hand to perform 13 tasks, focusing not only on the healthy hand but taking on a bilateral approach [129]. In the AWMF guideline, only the CAHAI-7 was used, which employs the first seven items. The scoring is similar to the FIM, utilizing a seven point scale with 13 being the minimum and 91 the maximum possible score. A higher score implies a higher level of functional independence [129].
- *Stroke Impact Scale (SIS):* The SIS provides a multidimensional tool combining the measurement of physical dimensions as well as other aspects of HRQoL of patients recovering from stroke in a self-report questionnaire, which consists of 59 questions covering eight domains (strength, hand function, mobility, ADL, emotion, memory, communication, and social participation) [130]. A five-point Likert scale is applied, showing the difficulties the patient had on performing these items. Scores of each domain are summed up to a maximum of 100. Higher scores reflect a greater self-reported level of health [131].
- *ABILHAND:* ABILHAND is a semi-structured based interview asking patients about the perceived difficulty on 23 bimanual items on a three level response scale ranging from zero to two. The higher the score the easier it was for the patient to perform the task without help [132].
- *Jebsen Hand Function Test (JTHFT):* This instrument presents a three-domain based system for assessing fine motor activity skills, weighted and non-weighted functional hand tasks while performing seven items of everyday activities [133]. A total score is formed by summing up all the times required to complete each task where a lower score is indicative of a higher unilateral hand function [134].

Further, there are less direct instruments assessing ADL such as the Arm Activity Ratio (AAR) measured by an accelerometer at the wrist side [135].

Körperfunktionen: z. B. FMA, MSS, WMFT

Body function and structure (BF) was defined as a relevant outcome evaluating the clinical benefit of using robotic devices in stroke rehabilitation. The AWMF guideline [4] described, among others, the following instruments hereby: Fugl-Meyer Assessment of Motor Recovery after Stroke (FMA) [136], Motor Status Scale (MSS) [137], Wolf Motor Function Test (WMFT) [138], Nottingham Sensory Assessment (NSA) [139], Rancho Functional Test for the Hemiplegic/Paretic Upper Extremity (RFTHUE) [140], Subscales of the Stroke Impact Scale (SIS) [141], Active range of motion (ROM) [128], Rehabilitation Engineering Laboratory Hand Function Test (RELHFT) [130], Stroke Impairment Assessment Set (SIAS) [128].

Further instruments (power, space within reach, joint stability scale) were described by the guideline, however, it was unclear as to whether these instruments were validated outcome measures.

Einschränkungen der Aktivität: z. B. ARAT, UEFT

Activity limitations (AL) is a further relevant outcome measure in assessing the patient's health and disability following a stroke [141]. It was measured, among others, by using the following tools [4]: Action Research Arm Test (ARAT) [142], Upper Extremity Function Test (UEFT) [143], Frenchay Arm Test (FAT) [144], Box and Block Test (BBT) [139].

Muskelkraft: v. a. Motricity Index

Muscle strength (MS) was used as relevant (secondary) outcome of interest. It is somewhat a more indirect outcome measure, but it may be still further relevant since muscle weakness is a clinical consequence of stroke patients which often leads to reduced physical activity and reveals neurologic impairments [145, 146]. MS can be measured using the following instruments: Trunk Control Test (TCT) [147], Modified Ashworth Scale (MAS) [148], MI [91], Jamar Hand Dynamometer (JHD) [149], Medical Research Council Manual Muscle Testing scale (MRC-Scale) [150], and Motor Power Score (MP) [151].

Further instruments ("mean strength") were described by the guideline, however, it was unclear as to whether these instruments were validated outcome measures.

It is to be noted that the outcomes of interest (and instruments) sometimes overlap.

Patient*innenzufriedenheit und Lebensqualität: verschiedenste Fragebögen

For patient satisfaction (PSA), there are various scientific tools available, however, we also considered discontinuation due to the study device or a simple visual analogue scale measuring tolerance or acceptance as eligible for this outcome.

As studies have proven that cerebrovascular accidents affect numerous aspects of Health-related Quality of Life (HRQoL) [152] the effect of robotics on HRQoL and PSA were considered as relevant outcomes. HRQoL can be assessed with generic (e.g., EQ-5D-5L [92], SF-36 [93]) or stroke specific instruments (e.g., through the SIS).

4.1.2 Safety

Sicherheit: unerwünschte und schwerwiegende unerwünschte Nebenwirkungen

The following outcomes were selected to evaluate the safety of the rehabilitation devices under evaluation:

- Adverse events (AE)
- Serious adverse events (SAE)
- Device-related adverse events.

The definitions of AEs/SAEs and device-related AEs/SAEs of the European Commission guidelines on medical devices were applied [94]. It is noteworthy to state that the AWMF S3 guideline [4] did not clearly define whether the safety of these devices was assessed. Information on these outcomes were retrieved from the evidence tables that are accessible in the appendix of the guideline.

4.2 Included studies

Evidenzsynthese basiert auf 1 AMWF LL (2020): 411 RCT + 114 SR

For the evaluation of upper limb RAR and FES assisted upper limb stroke rehabilitation, one recent AWMF S3 guideline (2020) [4] was included. The AWMF S3 guideline included 411 RCTs and 114 systematic reviews (SRs) for assessing the effectiveness of numerous different interventions that may be used in upper limb stroke rehabilitation [4].

RAR: 1 Cochrane Review und 16 RCT FES: 9 RCT

After applying our inclusion criteria, only the results of one Cochrane review and 16 primary studies comparing RAR to standard rehabilitation and nine RCTs evaluating the clinical benefit of FES are described in this chapter.

The systematic search of the guideline in the database PubMed covered the periods March 2009, November 2013 and July 2017 [4]. Further searches were conducted until inception, but these follow up searches were not described in further detail by the guideline.

Setting: stationär und ambulant

The overall setting of the guideline takes place in an inpatient, rehabilitative and outpatient care context [4]. No further differentiation was provided on how many studies were conducted in each single context for both RAR and FES.

Methodological quality/RoB assessment

LL qualitativ hochwertig nach AGREE-II

Using the Appraisal of Guidelines for Research And Evaluation Instrument (AGREE II) for assessing the methodological quality of the AWMF guideline resulted in the highest possible overall score (7/7). Thus, the guideline is recommended for use. Details on the AGREE II assessment can be taken from Table A-2.

Qualitätsbeurteilung der Studien mittels PEDro Scale

The methodological quality of the included RCTs was assessed by the guideline using a modified version of the PEDro scale [81] being informed by the Oxford Scale [83]. Based on these questions, the overall quality of the individual studies was rated (++, +, -, --). Subsequently, the guideline authors classified the RCTs according to the CEBM classification (1b or 2b).

Synthesis

qualitative Evidenzsynthese

The guideline conducted a qualitative evidence synthesis using the GRADE scheme (Grades of Recommendation, Assessment, Development and Evaluation) [4]. However, only the overall certainty of the body of evidence for the interventions are reported, without GRADE summary of finding tables and/or information on the certainty of the evidence on the outcome level.

Anwendung von GRADE

The guideline´s clinical recommendation and assessment of certainty of the evidence based on GRADE are structured according to the disease stage.

Funding

transparente Beschreibung möglicher COIs

Sponsors of the guideline were the Federal Association for Rehabilitation e. V. and the German Society for Neurorehabilitation e. V. (DGNKN). Potential conflict of interests of authors were adequately reported: consultant (1/10), industry advisory board (2/10), educational activities (6/10), author/co-author (7/10), research projects/ongoing clinical trials (2/10) and indirect interests (1/10).

Funding der Primärstudien nicht berichtet

Information on funding of included primary studies was not reported by the AWMF S3 guideline [4].

Further notes

Inclusion criteria were aligned with the inclusion criteria of this systematic review.

Follow-up data of primary studies is not consistently reported across studies.

4.3 Effectiveness and safety of robot assisted upper limb stroke rehabilitation

4.3.1 Included Studies

Study characteristics

The guideline included one Cochrane systematic review and 16 RCTs (n= 1,393) fulfilling our inclusion criteria.

LL identifizierte 1 Cochrane SR und 16 RCTs mit 1b LoE

The LoE of these studies was rated to be 1b LoE by the guideline (++ for 1 RCT and + for the remaining 15 RCTs).

Of all 16 RCTs, 13 evaluate robotic devices assisting shoulder and elbow movements. Five of them report on the MIT-MANUS, two on MIME, three on NeRoBot, and each one on Pneu-Wrex, ARMin and Haptic Master Robot respectively [4]. Forearm and wrist movements can be practised with the Bi-Manu Track. Evidence for that was found in one RCT [4]. The impact of robotic assisted rehabilitation on finger motion is reported for the intervention Hand Mentor in one trial [4]. Further, one RCT insufficiently reported on which robotic device was used [4].

RAR für Schulter/Ellbogen: 13 RCTs
Unterarm- und Handgelenk: 1 RCT
Fingerbewegung: 1 RCT
unzureichende Beschreibung in 1 RCT

Patient characteristics, stroke stadium and setting

Three studies (n=75) enrolled subacute stroke patients and further seven studies (n=356) enrolled chronic stroke patients. The remaining six studies had patients in mixed stages: patients with acute/subacute stroke were enrolled in one study (n=34), subacute/chronic stroke patients were enrolled in four studies (n=158), and one further study (n=770) did not filter the eligible studies according to the phase of stroke.

Stadium der Schlaganfallrehab: subakut in 3 RCTs
chronisch in 7 RCTs
gemischtes Stadium in restlichen Studien

The severity/level of impairment was moderate to severe in the studies identified by the AWMF S3 guideline [4].

Grad der Beeinträchtigung: moderat bis schwerwiegend

The specific setting (inpatient/outpatient) of the included studies was not reported by the guideline [4].

Setting: NR

A brief summary table of the studies identified by the AWMF S3 guideline are included at the end of this section (Table 4-1). Data-extraction-tables of the individual studies can be found in the appendix of the AWMF S3 guideline [4][31].

[31] The appendix is accessible online ("Link zu den Evidenztabellen"): https://www.awmf.org/leitlinien/detail/ll/080-001.html (accessed on 08.08.2020).

4.3.2 Results

AWMF S3 LL: hohe Qualität der Evidenz für Nutzen bei Pts im subakuten Stadion und schweren Armparesen

The AWMF guideline found high quality evidence that arm RAR for subacute stroke patients with severe arm paresis can improve selective mobility (grade of recommendation: B) [4]. For chronic stroke patients, the quality of evidence of a beneficial effect was rated low (grade of recommendation: 0) [4].

Since the number of specific movements to be conducted in the robotic therapy is limited, studies revealed that additional non-device based therapeutic measures should supplement the treatment plan. Yet, the quality of evidence is graded very low (grade of recommendation: B) [4].

Effectiveness

1 Cochrane SR: 45 RCTs 1.619 Pts

Verbesserung bei ADL, Armfunktionalität und Muskelstärke

The guideline found one recent Cochrane systematic review published in 2018: the SR included 45 RCTs with overall 1,619 study participants. The review found high quality evidence supporting arm robot therapy in comparison to control groups (other devices, therapy without devices, no therapy after a training) for at least 3x/week 20-90 minutes therapy over 2-12 weeks both in terms of ADL, arm function and strength, with standardised mean differences of 0.31 (95%CI: 0.09-0.52; p=0.0005; 24 studies with 957 participants), 0.32 (95%CI: 0.18-0.46; p<0.0001; 41 studies with 1452 participants) and 0.46 (95%CI 0.16-0.77; p=0.003; 23 studies with 826 participants) respectively.

Function[32]

16 RCTs (1b LoE): Schulter/Ellbogenbewegung: 13 RCTs

For **shoulder and elbow movements,** the guideline found 13 RCTs evaluating functional outcomes of the MIT-MANUS (5 studies), MIME (2 studies), NeRoBot (3 studies) and Pneu-Wrex (1 study), ARMin (1 study), and Haptic Master Robot (1 study).

Aktivitäten des Alltags: + in 6 RCTs Ø in 3 RCTs

ADL was reported in nine out of 13 RCTs identified by the AWMF S3 guideline (different stages; n= 1,122): six studies (n=962; four different instruments, subacute/chronic stage) showed a statistically significant difference measured by four different instruments in favour of RAR up to eight months follow up. Of note is that one of these studies (n=770) measured this endpoint as a secondary outcome and the AWMF guideline authors judged this difference to be not clinically relevant [1] and one of these studies didn't find a statistically significant difference for all outcome instruments used to measure ADL. Further three studies enrolling patients in the subacute or chronic stage of stroke did not find statistically significant differences between RAR and standard rehabilitation measured by two instruments.

Körperfunktionalität: + in 7 RCTs Ø in 6 RCTs

BF was reported by all of the identified 13 RCTs (n=1,393) measured by various instruments [4]: seven RCTs (n=1,005) that enrolled stroke patients in different stages showed a statistically significant difference in favour of RAR up to three years follow up measured by three different instruments. Of note is that one of these studies (n=770) measured this endpoint as a secondary outcome and the guideline authors judged this difference to be not clinically relevant [4] and four of these studies favouring RAR did not find statistically significant difference for all outcome instruments used to measure BF. Six further studies did not find a statistically significant difference between intervention and control groups.

[32] D0011 – What is the effect of upper limb RAR on patients' body functions?, D0016 – How does the use of upper limb RAR affect activities of daily living?

AL was reported by five out of 13 included RCTs (subacute/acute/chronic stage): four studies (n=853) did not find a statistically significant difference between the intervention and control groups measured by three different instruments. The remaining study (n=21) did not report statistical data on the group difference.

Einschränkung der Aktivität: Ø in 4 Studien; ND in 1 RCTs

MS was reported in nine out of 13 RCTs (n=341) enrolling stroke patients in different stages: five of these studies (n=185) found statistically significant differences in favour of RAR compared to conventional therapy on four different instruments up to eight months follow up. Of these, three studies didn't find a statistically significant difference for all outcome instruments used to measure MS. Three further studies did not find statistically significant differences between intervention and control groups in BF. One study found the standard rehabilitation group to increase more in strength measured by one out of two instruments used to measure MS.

Muskelkraft: + in 5 RCTs; Ø in 3 RCTs; - in 1 RCT

For **forearm and wrist movements,** the guideline found one RCTs evaluating functional outcomes after rehabilitation with the Bi-Manu Track.

Unterarm- und Handgelenkbewegung: 1 RCT;

ADL was reported by the RCT (chronic; n=20) utilising three different instruments: statistically significant higher improvement for RAR was evident in ADL by two out of three of the utilised instruments [4].

Aktivitäten des Alltags: + in 1 RCT

BF was reported in the identified RCT utilising one instrument: a statistically significant higher improvement in favour of the robotic therapy for chronic stage patients was found hereby [4].

Körperfunktionalität: + in 1 RCT

The endpoint *AL* was not reported in the RCT included by the guideline [4].

MS was not reported in the RCT identified by the guideline [4].

For **finger movements,** the guideline [4] found one RCT (subacute and chronic; n=21) evaluating the functional outcomes after rehabilitation with the Hand Mentor robot.

Fingerbewegungen: 1 RCT: ND

For the endpoint *ADL* and *BF*, the RCT identified by the guideline [4] did not report statistical data of the group difference.

AL and *MS* were not reported by the RCT identified by the guideline [4].

The guideline [4] found further one RCT (subacute; n=127) that reported on functional outcomes, but insufficiently specified which robot was used (**no classification**).

1 weitere unklassifizierte RCT:

ADL was not reported in this RCT [4].

BF was reported in the RCT (chronic; n=127) included by the guideline. At 36 weeks follow up, statistically significant differences were found in favour of the RAR in comparison to standard rehabilitation in two outcome instruments used to assess BF. At 12 weeks follow-up, statistically significant differences were only found in one outcome instrument used to assess BF.

Körperfunktionalität: + in 1 RCT

AL and *MS* were not reported by the RCT identified by the guideline [4].

Health-related quality of life[33]

Lebensqualität in 2 RCTs: Ø

The effect of the intervention on generic health-related quality of life (HRQoL) was evaluated in two RCTs identified by the guideline [4].

For **shoulder and elbow movement robots,** HRQoL was reported by two RCTs that were identified by the guideline [4]: One study (acute/subacute/chronic; n=770) did not find a statistical significant difference between the MIT MANUS and standard rehabilitation by using the pain numerical rating scale of the EQ-5D-5L to estimate HRQoL at baseline, after three and after six months. Another RCT (chronic; n=22) measured the health related quality of life with the EQ-5D and SF-36 questionnaire: the study found no statistically significant between group difference by using one generic instrument (EQ-5D) and a statistically significant difference in a sub-score (delta physical health scores) of the SF-36 favouring the Haptic Master-Robot when compared to the T-TOAT method.

For the other robotic devices focusing on **forearm and wrist movement**, **finger movement**, and these that were **not sufficiently classified** by the studies, no evidence was found on this endpoint by the guideline [4].

krankheitsbezogene Lebensqualität: 3 RCTs

The effect of the intervention on disease specific HRQoL[34] was evaluated in three RCTs (n=169) by the guideline [4].

Schulter/Ellbogen: Ø in 1 RCT

For **shoulder and elbow movement robots,** disease-specific QoL was reported by one study (chronic; n=21) identified by the guideline [4]: no statistically significant group difference for disease specific QoL measured by the Beck Depression Inventory and the pain scale of the FM test between patients receiving a rehabilitation with the MIT-Manus and movement-based treatment respectively.

For **forearm and wrist movement robots,** no evidence was found on this endpoint by the guideline [4].

Fingerbewegung: Ø stat. signifikante Unterschiede nur in Subscales zugunsten (Stimmung) und zuungunsten (Soziale Partizipation) der Intervention

With respect to robotic devices used for **finger movement** rehabilitation, the guideline identified one RCT (subacute and chronic; n=21) comparing disease-specific quality of life between robotic training with the Hand Mentor and repetitive task practice and therapist repetitive task practice alone in subacute and chronic stroke patients: Mood and social participation were associated with a statistically significant difference between control and intervention group. While a statistically significant higher average change on mood rating in contrast to the comparator was observed at post-intervention, the average change in social participation was significantly higher in the control group from pre-intervention to follow-up [4].

No classification

1 weitere unklassifizierte RCT: soziale Partizipation: +

The RCT (n=127) that did not specify the specific robotic rehabilitation used reported on disease-specific quality of life in chronic stroke patients: patients receiving RAR showed a statistically significant higher improvement in social participation (SIS-social participation score) than conventional therapy [4].

[33] D0012 – What is the effect of upper limb RAR on generic health-related quality of life?

[34] D0013 – What is the effect of robot assisted stroke rehabilitation on disease-specific quality of life?

Patient satisfaction[35]

Zufriedenheit in 2 RCTs

Satisfaction of patients with the technology was reported in two out of 16 RCTs included by the guideline [4].

hohe Akzeptanz von RAR

Both of the RCTs (n=69; acute and subacute patients) assessed tolerance and acceptance of the NeRoBot device through a Visual Analog Scale (VAS): In both studies the robotic therapy showed a high degree of tolerance among patients, reaching a mean score of 78.7/100 and 8.2/10 respectively. Eleven patients were willing to include NeReBot in their post stroke rehabilitation scheme [4].

Safety[36]

Sicherheit

The guideline identified one Cochrane systematic review and six out of 16 LoE: 1b) RCTs reported on AEs [4].

1 Cochrane Review: vergleichbare Sicherheit

Based on the Cochrane review that was identified by the guideline [4], arm-robot therapies were found to be safe and well accepted by the patients; that is, comparable to control therapies, with a risk difference of 0.00 (95%CI –0.02-0.02, p=0.93).

6 RCTs berichten Sicherheitsendpunkte:

Of the 16 RCTs identified by the guideline, six studies reported on safety outcomes. In one study (acute/subacute/chronic; n=770), 39 participants receiving MIT MANUS stated having 43 SAEs, whereas 29 were recorded for 20 participants in the standard rehabilitation group. None of these side effects was related to the trial intervention. In the second study (subacute; n=35), assessing rehabilitation with the NeReBot versus standard rehabilitation and sham therapy, patients experienced no AEs at all in the intervention group. Besides, no difference was found with respect to joint or tendon-related pain in the shoulder, wrist, or hand in another RCT (acute/subacute; n=34) as well.

SAEs berichtet in 5 RCTs: keine schwerwiegenden unerwünschten Nebenwirkungen durch RAR

milde Nebenwirkungen durch RAR in 1 RCT

Schmerzen: Ø

Minor AEs related to the intervention were experienced by two participants in the ARMin group in another study (chronic; n=77) but no serious AE occurred. Another study stated that no AEs were recorded for any chronic stroke patients (n=11) receiving training with the Haptic Master robot [4]. One further RCT (chronic; n=127) included by the guideline did not specify the specific robotic device: the study reported no treatment related serious side effects. AEs associated with the treatment, were mild which were reported for twelve participants in the robot group and nine in the intensive comparison therapy group. Likewise, no significant differences between groups on the pain scale and spasticity were identified [4].

[35] D0017 – Was the use of upper limb RAR worthwhile?/ Were patients satisfied with the technology?

[36] C0008 – How safe is upper limb RAR in comparison to standard rehabilitation alone?

Table 4-1: Summary table of the evidence synthesis of the AWMF S3 guideline: RCTs (LoE 1b only) evaluating the clinical benefit of the use of robotics for upper limb stroke rehabilitation

LoE	Autor/ year	Intervention	Sample Size (IG/CG)	Stage	ADL	BF	AL	MS	AE	QoL/PSA
Shoulder and elbow movements										
1b, +	Volpe et al., 2000	■ MIT MANUS + Standard rehabilitation (rehabilitation therapy) vs. ■ Standard rehabilitation + "sham"-therapy	56 (30/26)	Subacute/chronic stroke with severe arm paresis or plegie	+ (FIM, FU n.r.)	+ (MSS, FU n.r.)		+ (MP, FU n.r.)		
1b, +	Volpe et al., 1999	■ MIT-MANUS + Standard rehabilitation (physio- and occupational therapy) vs. ■ Standard rehabilitation + placebo	20 (n. r.)	Subacute stroke with arm paresis		+ (MSS, PI, 3 yrs. FU)		+ (MP, PI)		
1b, ++	Rodgers et al., 2019	■ MIT MANUS or enhanced upper limb therapy (EULT) vs. ■ Standard rehabilitation (NHS poststroke care[37])	770 (516/254)	Acute/subacute/ chronic stroke with moderate to severe arm paresis	+ (BI, SIS-ADL, 3 m. FU, 6 m. FU n. r.)	+ (FMA, 3 +, 6 m. FU)	**Ø** (ARAT, 3 +, 6 m. FU)		IG: 43 SAEs in 33 pts. CG: n. r.[38]	**Ø** (EQ-5D-5L, 3 +, 6 m. FU)
1b, +	Volpe et al., 2008	■ MIT-MANUS vs. ■ Standard rehabilitation (intensive upper extremity movement-based treatment)	21 (11/10)	Chronic stroke with moderate to severe arm paresis		**Ø** (FMA-WH, JSS, 3 m. FU)	**ND** (ARAT)	**Ø** (MAS, FU n .r., MP, 3 m. FU)		**Ø** (BDI, FU n .r.)
1b, +	Conroy et al., 2011	■ InMotion (=MIT MANUS) (planar reaching or combined planar + vertical) vs. ■ Standard rehabilitation (intensive conventional arm exercise)	62 (41/21)	Chronic stroke (moderate to severe arm paresis)		**Ø** (FMA, 12 w. FU)[39]				
1b, +	Burgar et al., 2011	■ MIME (low or high dose vs. ■ Standard rehabilitation (conventional therapy)	54 (36/18)	Subacute/chronic stroke with moderate to severe arm paresis or plegie	+ (FIM, post-hoc)	**Ø** (FMA, PI, 6 m. FU) (WMFT, 6 m. FU)		**Ø** (MRC, MP 6 m. FU + (MAS, 6 m. FU)		
1b, +	Lum et al., 2002	■ MIME therapy vs. ■ Bobath therapy + "sham"-therapy	27 (13/14)	Subacute/chronic stroke with severe arm paresis or plegie	+ (FIM, 6m.) **Ø** (BI, 6m.)[40]	**Ø** (FMA,, 6 m. FU) + (power, space within reach, FU n. r.)				

[37] Many stroke units achieve this target for physiotherapy and occupational therapy, but considerable variation exists in service provision after discharge

[38] None of the serious adverse events were related to a trial intervention

[39] WMFT and SIS as secondary outcomes measures were not mentioned in the guideline

[40] The guideline insufficiently reported on these results; hence, the primary study was retrieved and information was based on the primary study hereby.

LoE	Autor/ year	Intervention	Sample Size (IG/CG)	Stage	ADL	BF	AL	MS	AE	QoL/PSA
1b, +	Masiero et al., 2006	■ NeRoBot + Standard rehabilitation (multidisciplinary post-stroke rehabilitation) vs. ■ Standard rehabilitation + "sham"-therapy	20 (10/10)	Subacute stroke with moderate to severe arm paresis	+ (FIM, PI, 3 m. FU)	+ (FMA-SEC, 3 m. FU) Ø (FMA-WH, 3 m. FU)		Ø (upMI, PI, MRC-EW, 3 m. FU) + (upMI, 3 m. FU)		
1b, +	Masiero et al., 2007	■ NeReBo + Standard rehabilitation (Bobath therapy + occupational therapy) vs. ■ Standard rehabilitation + "sham"-therapy	35 (17/18)	Subacute stroke with moderate to severe arm paresis	+ (FIM, 3-8 m. FU)	+ (FMA-SEC, 3-8 m. FU) Ø (FMA-WH, 3-8 m. FU)		+ (MRC-D, 3-8 m. FU) Ø (MRC-BWF, MAS, TCT, 3-8 m. FU)	No AEs in IG occurred Ø (pain, PI, FU n. r)	VAS: mean score in IG: 78.7/100, PI)
1b, +	Masiero et al., 2014	■ NeReBot + Standard rehabilitation (rehabilitation treatment) vs. ■ Standard rehabilitation	34 (16/18)	Acute/subacute stroke with mild to severe arm paresis		Ø (FMA,, PI, 3-7. m. FU)	Ø (FAT, BBT, PI, 3-7. m. FU)	Ø (MAS, MRC, PI, 3-7. m. FU)	Ø (pain, PI, FU n. r.)	VAS; mean score in IG 8.2/10)
1b, +	Reinkensmeyer et al., 2012	■ Pneu-Wrex vs. ■ Standard rehabilitation (conventional table top therapy)	27 (13/14)	Chronic stroke with moderate to severe arm paresis	Ø (MAL, 24 sessions + 3 m. FU)	Ø (FMA, NSA, RFTHUE, 24 sessions + 3 m. FU)	Ø (BBT, 24 sessions + 3 m. FU)	Ø (JHD, 24 sessions + 3 m. FU)		
1b, +	Klamroth-Margansk et al., 2014	■ ARMin vs. ■ Standard rehabilitation (physical or occupational therapy)	77 (39/38)	Chronic stroke with moderate to severe arm paresis	Ø (MAL-QOM, FU n. r.)	+ (FMA, FU n. r.)[41] Ø (WMFT, SIS-pd, FU n. r.)		- (mean strength, FU n. r.) Ø (MAS, FU n. r.)	no SAEs occurred (IG: 2 pts. minor AEs related to I)	
1b, +	Timmermans et al., 2014	■ Haptic Master-Robot + T-TOAT method vs. ■ T-TOAT method	22 (11/11)	Chronic stroke with mild to moderate arm paresis	Ø (MAL, 6 m. FU)	Ø (FMA, 6 m. FU)	Ø (ARAT, FMA, 6 m. FU)		No AEs occurred	Ø (EQ-5D, FU n. r.) + (delta physical health score on SF-36, FU n. r.)
Forearm and wrist movements										
1b, +	Liao et al., 2012	■ Bi-Manu-Track + Standard rehabilitation (occupational therapy) vs. ■ Standard rehabilitation	20 (10/10)	Chronic stroke patients with moderate arm paresis	+ (AAR, MAL, FU n. r.) Ø (FIM, FU n. r.)	+ (FMA, FU n. r.)				

[41] Statistical but no clinical significant difference

LoE	Autor/ year	Intervention	Sample Size (IG/CG)	Stage	ADL	BF	AL	MS	AE	QoL/PSA
Finger movements										
1b, +	Kutner et al., 2010	■ Hand Mentor + Repetitive task practice (RTP) vs. ■ Therapist supervised RTP	21 (10/11)	Subacute and chronic stroke with moderate to severe arm paresis with some preserved hand function	**ND** (SIS-ADL/ IADL, PI)[42]	**ND** (SIS-hand function, PI)[43]				+ (SIS-mood, PI) - (SIS-social participation, PI)
No classification										
1b, +	Lo et al., 2010	■ Robot-assisted therapy or intensive comparison therapy vs. ■ Standard rehabilitation (customary care available to all patients)	127 (99/28)	Chronic stroke with moderate to severe paresis		**Ø** (FMA, WMFT, after 12 w.) + (FMA, 36 w. FU) + (SIS-motor function, after 12 w., 36 w. FU n. r.)			No SAEsrelated to device, mild AEs: IG: 12 in 50 pts, CG: 9 in 50 pts.	+ (SIS-social participation, after 12 w., 36 w. FU n. r.)

Source: References to the studies identified by the guideline [4] and rated with 1b LoE:

Burgar C., Lum P., Scremin A., Garber S., Loos H., 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;48:445-458. DOI: 10.1682/JRRD.2010.04.0062.

Conroy S. S., Whitall J., Dipietro L., Jones-Lush L. M., Zhan M., Finley M. A., et al. Effect of Gravity on Robot-Assisted Motor Training After Chronic Stroke: A Randomized Trial. Arch Phys Med Rehabil. 2011;92(11):1754-1761. DOI: https://doi.org/10.1016/j.apmr.2011.06.016.

Klamroth-Marganska V., Blanco J., Campen K., Curt A., Dietz V., Ettlin T., et al. Three-dimensional, task-specific robot therapy of the arm after stroke: a multicentre, parallel-group randomised trial. The Lancet Neurology. 2014;13(2):159-166. DOI: https://doi.org/10.1016/S1474-4422(13)70305-3.

Kutner N. G., Zhang R., Butler A. J., Wolf S. L. and Alberts J. L. Quality-of-life change associated with robotic-assisted therapy to improve hand motor function in patients with subacute stroke: a randomized clinical trial. Phys Ther. 2010;90(4):493-504. Epub 2010/02/25. DOI: 10.2522/ptj.20090160.

Liao W.-w., Wu C.-Y., Hsieh Y.-W., Lin K.-c. and Chang W.-Y. Effects of robot-assisted upper limb rehabilitation on daily function and real-world arm activity in patients with chronic stroke: A randomized controlled trial. Clin Rehabil. 2011;26:111-120. DOI: 10.1177/0269215511416383.

Lo A. C., Guarino P. D., Richards L. G., Haselkorn J. K., Wittenberg G. F., Federman D. G., et al. Robot-assisted therapy for long-term upper-limb impairment after stroke. N Engl J Med. 2010;362(19):1772-1783. Epub 2010/04/20. DOI: 10.1056/NEJMoa0911341.

Lum P. S., Burgar C. G., Shor P. C., Majmundar M. and Van der Loos M. Robot-assisted movement training compared with conventional therapy techniques for the rehabilitation of upper-limb motor function after stroke. Arch Phys Med Rehabil. 2002;83(7):952-959. Epub 2002/07/05. DOI: 10.1053/apmr.2001.33101.

Masiero S., Armani M., Ferlini G., Rosati G. and Rossi A. Randomized trial of a robotic assistive device for the upper extremity during early inpatient stroke rehabilitation. Neurorehabil Neural Repair. 2014;28(4):377-386. Epub 2013/12/10. DOI: 10.1177/1545968313513073.

[42] Not clinically significant

[43] Clinical significance demonstrated in FU

Masiero S., Celia A., Armani M. and Rosati G. A novel robot device in rehabilitation of post-stroke hemiplegic upper limbs. Aging Clin Exp Res. 2006;18(6):531-535. Epub 2007/01/27. DOI: 10.1007/bf03324854.

Masiero S., Celia A., Rosati G. and Armani M. Robotic-Assisted Rehabilitation of the Upper Limb After Acute Stroke. Arch Phys Med Rehabil. 2007;88(2):142-149. DOI: https://doi.org/10.1016/j.apmr.2006.10.032.

Reinkensmeyer D. J., Wolbrecht E. T., Chan V., Chou C., Cramer S. C. and Bobrow J. E. Comparison of three-dimensional, assist-as-needed robotic arm/hand movement training provided with Pneu-WREX to conventional tabletop therapy after chronic stroke. Am J Phys Med Rehabil. 2012;91(11 Suppl 3):S232-S241. DOI: 10.1097/PHM.0b013e31826bce79.

Rodgers H., Bosomworth H., Krebs H. I., van Wijck F., Howel D., Wilson N., et al. Robot assisted training for the upper limb after stroke (RATULS): a multicentre randomised controlled trial. Lancet. 2019;394(10192):51-62. Epub 2019/05/28. DOI: 10.1016/s0140-6736(19)31055-4.

Timmermans A., Lemmens R., Monfrance M., Geers R., Bakx W., Smeets R., et al. Effects of task-oriented robot training on arm function, activity, and quality of life in chronic stroke patients: A randomized controlled trial. Journal of neuroengineering and rehabilitation. 2014;11:45. DOI: 10.1186/1743-0003-11-45.

Volpe B. T., Lynch D., Rykman-Berland A., Ferraro M., Galgano M., Hogan N., et al. Intensive sensorimotor arm training mediated by therapist or robot improves hemiparesis in patients with chronic stroke. Neurorehabil Neural Repair. 2008;22(3):305-310. Epub 2008/01/11. DOI: 10.1177/1545968307311102.

Volpe B., Krebs H., Hogan N., Edelsteinn L., Diels C. and Aisen M. Robot training enhanced motor outcome in patients with stroke maintained over 3 years. Neurology. 1999;53:1874-1876. DOI: 10.1212/WNL.53.8.1874.

Volpe B., Krebs H., Hogan N., Otr L., Diels C. and Aisen M. A novel approach to stroke rehabilitation: Robot-aided sensorimotor stimulation. Neurology. 2000;54:1938-1944. DOI: 10.1212/WNL.54.10.1938.

*1. **Explanations:** +/- significant effects for/against the former additional intervention, Ø no significant group differences ND = no statistical data available or reported (for group comparison)*

*2. **Abbreviations:** AAR – Arm Activity Ratio; ADL – Activities of daily living; AE – adverse event; AL – Activity limitations; ARAT – Action Research Arm Test; BBT – Box and Block Test; BDI – Beck Depression Inventory; BF –Body function and structure; BI – Barthel Index; BWF – Biceps and Wrist Flexor; CAHAI – Chedoke Arm and Hand Activity Inventory; CG – Control group; CMSA – Chedoke McMaster Stroke Assessment; CMSMR – Chedoke McMaster Stages of Motor Recovery; D – Deltoid; EW – Elbow, Wrist; FAT – Frenchay Arm Test; FIM – Functional Independence measure; FMA – Fugl Meyer Assessment; FU – Follow-up; IG – Intervention group; JHD – Jamar Hand Dynamometer; JSS – Joint Stability Scale; JTHFT – Jebsen Taylor Hand Function Test; LS – Likert Scale; M – month; MAL – Motor Activity Log Scale; MAL-AOU – Motor Activity Log Scale Amount of Use; MAL-QOM – Motor Activity Log Scale Quality of Movement; MAS – Modified Ashworth Scale; MBI – Modified Barthel Index; MI – Motricity Index; MP – Motor Power Score; MRC-Scale – Medical Research Council Manual Muscle Testing Scale; MS – Muscle Strength; MSS – Motor Status Score; NSA – Nottingham Sensory Assessment; PI – Post-intervention; PSA – Patient satisfaction; QoL – Quality of Life; RFTHUE – Rancho Functional Test for the Hemiplegic/Paretic Upper Extremity; RTP – Repetitive Task Practice; SA – Self-Assessment; SAE – Serious adverse event; SEC – Shoulder, Elbow and Coordination; SIS – Stroke Impact Scale (domains: strength, hand function, ADL/IADL, mobility, communication, emotion, memory and thinking, and participation); SISpd – Stroke Impact Scale physical domain; SoC – Standard rehabilitation; TCT – Trunk Control Test; upMI – Upper-Motricity Index; W – Week; WF – Wrist flexors; WH – Wrist, Hand; WMFT – Wolf Motor Function Test.*

4.4 Effectiveness and safety of functional electrical stimulation (FES) for upper limb stroke rehabilitation

4.4.1 Included studies

Study characteristics

LL identifizierte 9 RCTs mit 1b LoE

The AWMF S3 guideline published in 2020 included nine RCTs (n=237[44]) evaluating the clinical benefit of FES.

The LoE was judged to be 1b for these nine RCTs by the guideline (+ for 4 RCT, n. r. in 1 RCT and – in 4 RCTs[45]).

Of these, one study evaluated the use of EMG-triggered FES, and four studies evaluated the comparative effectiveness of multi-channel FES in comparison to standard rehabilitation. For further four studies, the specific FES modality was not reported by the guideline [4].

Patient characteristics, stroke stadium and setting

7/9 RCTs untersuchten FES bei Pts in subakutem Stadium

Seven studies enrolled patients in the subacute stroke stadium, whereas chronic stroke patients were enrolled in the remaining two studies [4].

The severity/level of impairment was moderate to severe in the RCTs identified by the guideline [4].

The specific setting (inpatient/outpatient) of the included studies was not reported by the guideline [4].

diverse FES Modalitäten

The guideline insufficiently reported on the specific FES modalities: e.g., the product name was reported for 3/9 studies only and it was not clearly described whether FES was used for a specific body part (e.g., hand, shoulder) or whether FES was used more broadly for the whole arms. Hence, the description of the evidence describes the evidence for all RCTs that were identified by the guideline [4].

A brief summary table of the studies identified by the AWMF S3 guideline are included at the end of this section (Table 4-2). Data-extraction-tables of the individual studies can be found in the appendix of the AWMF S3 guideline [4][46].

[44] For one study, it was not reported whether it was judged to be a 1b RCT. We included it based on the provided evidence table.

[45] Although these studies were rated with a "-", the overall classification was still 1b in the guideline. According to the described methods, at least a "+" rating is needed for a 1b rating.

[46] The appendix is accessible online ("Link zu den Evidenztabellen"): https://www.awmf.org/leitlinien/detail/ll/080-001.html.

4.4.2 Results

AWMF S3 LL:

niedrige Qualität der Evidenz,

dass FES zur OE Rehabilitation bedingt eingesetzt werden kann

According GRADE, the AWMF S3 [4] guideline found low quality evidence demonstrating that FES, indicated for patients with severe incomplete hand paresis and partially preserved (proximal) motor function, can be used for inducing grasping and releasing or finger and hand extension combined with training of everyday activities. This applies in particular if the treatment aims to improve selective mobility or arm activities and patients are willing to train one to two hours with FES. Further low quality evidence suggests that FES can also be considered for shoulder and elbow movements.

Similarly, low quality evidence was found by the guideline [4] that FES can be considered for shoulder and elbow movements.

Further, very low quality evidence was found by the guideline [4] showing that FES could be performed in small groups, for some patients also possibly at home.

Based on expert opinion, the guideline further stated that contraindications have to be noted: cardiac and brain pacemakers, potentially life-threatening heart rhythm disturbances, epileptic seizures in the recent past, metal implants in the treated arm.

Clinical effectiveness

Function[47]

9 RCTs

All of the nine primary studies identified by the guideline reported on functional outcomes after FES upper limb stroke rehabilitation.

Aktivitäten des Alltags:
+ in 1 RCT
Ø in 2 RCTs

ADL was reported by three out of nine studies that were identified by the guideline [4]: One RCT (subacute; n=46) evaluating a 2-channel found a statistically significant higher improvement favouring the FES group over standard rehabilitation alone. The remaining two studies, with 24 and 21 enrolled patients respectively found no statistically significant difference when comparing FES to standard rehabilitation in subacute stroke patients with severe arm paresis.

Körperfunktionalität:
+ in 5 RCTs
Ø oder ND in 3 RCTs

BF was reported in eight out of nine studies (subacute and chronic; n=196) that were identified by the guideline [4]: five RCTs found statistically significant differences in BF measured by various different instruments when comparing different modalities of FES to standard rehabilitation. Of these, one study didn't find a statistically significant difference for all outcome instruments used to measure BF. One further study (n= 23) did not find statistically significant differences between the additional use of FES compared to standard rehabilitation and for further two studies, statistical data on the group difference was not reported.

Einschränkung der Aktivität:
+ in 3 RCTs
Ø oder ND in 2 RCTs

AL was reported by five out of nine studies (subacute and chronic; n=131) that were identified by the guideline [4]: three studies found a statistically significant difference favouring FES assisted stroke rehabilitation (although one study did not find statistically significant differences in all instruments used to measure AL). The remaining two studies either did not find a statis-

[47] D0011 – What is the effect of upper limb FES on patients' body functions?, D0016 – How does the use of upper limb FES affect activities of daily living?

tically significant difference hereby or did not report statistical data for the group comparison. Numerous different outcome instruments were used to measure AL by these studies.

Muskelkraft: + in 1 RCT Ø oder ND in 3 RCTs

MS was reported by four out of nine studies (n=111; subacute and chronic stroke patients) that were identified by the guideline [4]: One study found a statistically significant difference favouring additionally using FES in comparison to standard rehabilitation and further two studies did not find a statistically significant difference hereby. One further study did not report statistical data for the group difference.

Health-related quality of life[48]

No evidence was found to answer these research questions.

Patient satisfaction[49]

PSA in 1 RCT: hohe Compliance

In one study (n=22) that was identified by the guideline [4], patients receiving the NESS Handmaster™ reported a high level of compliance. No treatment drop-outs occurred.

Safety[50]

Sicherheit nur in 2 RCTs berichtet: keine AEs in 1 RCT

Schulterschmerz: Ø in 1 RCT

The guideline [4] found sparse data on the safety of the devices: Overall two RCTs that were not classified by the guideline [4] reported on safety. One of these studies (n=22) related to the NESS Handmaster™ demonstrated that no AEs in either group occurred. Besides, pain and hand oedema were assessed as a secondary endpoint. However, no statistical data on group difference was demonstrated. Another study (n=23) further noted that there was no statistically significant group difference in shoulder pain score measured with the CMSA, without reporting on AEs as such.

[48] D0012 – What is the effect of upper limb FES on generic health-related quality of life?,
D0013 – What is the effect of upper limb FES on disease-specific quality of life?

[49] D0017 – Was the use of upper limb FES worthwhile?

[50] C0008 – How safe is upper limb FES in comparison to standard rehabilitation?

Table 4-2: Summary table of the evidence synthesis of the AWMF S3 guideline: RCTs (LoE 1b only) evaluating the clinical benefit of FES for upper limb stroke rehabilitation.

LoE	Autor/ year	Intervention	Sample size (IG/CG)	Stadium	ADL	BF	AL	MS	AE	QoL/PSA
1b, +	Shindo et al., 2011	■ EMG-triggered FES + SoC (physical therapy + occupational therapy) vs. ■ SoC	24 (12/12)	Subacute stroke with severe finger extensor paresis but some preserved muscle activity of the extensors	**Ø** (MAL, FU n. r.)	+ (FM, FU n. r.)	+ (ARAT, FU n. r.)			
n. r.	Popovic et al., 2004[51]	■ Multi-channel FES vs. ■ Task-oriented training without FES	41 (19/22)	Subacute stroke with arbitrary motor activity of the paretic hand			**ND** (UEFT, SA, FU n. r.)			
1b, -	Tarkka et al., 2011	■ FES (Actigrip®) (4-channel FES) + SoC (physical therapy) vs. ■ SoC	20 (10/10)	Chronic stroke with severe arm paresis		**ND** (WMFT, 6 m. FU)				
1b, -	Hara et al., 2008	■ Mulit-channel FES + SoC (occupational therapy + HEP) vs. ■ SoC	20 (10/10)	Chronic stroke with moderate to severe spastic upper extremity impairments of either shoulder or wrist/hand		+ (active ROM (W+F, S) FU n. r.) **ND** (10-CMT, 9-PHT, SIAS, FU n. r.)		**ND** (MAS, PI, FU n. r.)		
1b, +	Lin and Yan, 2011	■ FES (neuromuscular electrical stimulation; 2-channel Respond Select II stimulator) + SoC (physical therapy + occupational therapy) vs. ■ SoC	46 (23/23)	Subacute stroke with moderate to severe arm paresis	+ (MBI, 1 + 3 + 6 m. FU)	+ (FM, 1 + 3 + 6 m. FU)		**Ø** (MAS, 1 + 3 + 6 m. FU)		
1b, +	Ring et al., 2005	■ NESS Handmaster™ + SoC (physical and occupational therapy) vs. ■ SoC	22 (11/11)	Subacute stroke with moderate to severe arm paresis		**ND**[52] (active motion (SF, WE, WF), FU n. r.)	+ (BBT, JTHFT, FU n. r.)	+ (spasticity, FU n. r.)	no AEs occurred **ND** (pain, FU n. r)	High compliance in IG
1b, +	Chan et al., 2009	■ FES (functional electric stimulation with an intensity that elicited muscle movement for hand opening)+ SoC (occupational therapy) vs. ■ SoC + placebo	20 (10/10)	Subacute stroke with arm paresis and the inability to extend fingers		+ (FM, FTHUE, active ROM (WE), PI, FU n. r.)				
1b, -	Mangold et al., 2009	■ FES (reach, grab, release of objects, stimulation of the anterior part of the deltoid muscle, triceps muscle brachii, finger extensors and -flexors + SoC (occupational therapy)) vs. ■ SoC	23 (12/11)	Subacute stroke with severe to complete arm and/or hand paresis		**Ø** (EBI, PI, FU n. r.)	**Ø** (CMSA (arm+hand function), PI, FU n. r.)	**Ø** (MAS, PI, FU n. r.)	**Ø** (CMSA shoulder pain)	

[51] Results of 3 w. and 6 m. FU reported in Popovic et al., 2002 (n=16) and Popovic et al., 2003 (n=28)

[52] Unclear reported in guideline

LoE	Autor/ year	Intervention	Sample size (IG/CG)	Stadium	ADL	BF	AL	MS	AE	QoL/PSA
1b, -	Thrasher et al., 2008	■ FES (anterior or posterior deltoid, triceps and/or biceps for proximal movements or wrist or finger flexors and extensors for rough and fine gripping tasks+ SoC (occupational + physiotherapy) vs. ■ SoC	21 (10/11)	Subacute stroke with severe to complete arm paresis	Ø (FIM, FU n. r.)	+ (RELHFT[53] BI, FU n. r.) Ø (FM, RELHFT[54], FU n. r.)	+ (CMSMR, FU n. r.)			

Source: References to the studies identified by the guideline [4] and rated with 1b LoE:

Chan M. K., Tong R. K. and Chung K. Y. Bilateral upper limb training with functional electric stimulation in patients with chronic stroke. Neurorehabil Neural Repair. 2009;23(4):357-365. Epub 2008/12/17. DOI: 10.1177/1545968308326428.

Hara Y., Ogawa S., Tsujiuchi K. and Muraoka Y. A home-based rehabilitation program for the hemiplegic upper extremity by power-assisted functional electrical stimulation. Disabil Rehabil. 2008;30(4):296-304. Epub 2007/09/14. DOI: 10.1080/09638280701265539.

Lin Z. and Yan T. Long-term effectiveness of neuromuscular electrical stimulation for promoting motor recovery of the upper extremity after stroke. J Rehabil Med. 2011;43(6):506-510. Epub 2011/05/03. DOI: 10.2340/16501977-0807.

Mangold S., Schuster C., Keller T., Zimmermann-Schlatter A. and Ettlin T. Motor training of upper extremity with functional electrical stimulation in early stroke rehabilitation. Neurorehabil Neural Repair. 2009;23(2):184-190. Epub 2009/02/05. DOI: 10.1177/1545968308324548.

Popovic D. B., Popovic M. B., Sinkjaer T., Stefanovic A. and Schwirtlich L. Therapy of paretic arm in hemiplegic subjects augmented with a neural prosthesis: a cross-over study. Can J Physiol Pharmacol. 2004;82(8-9):749-756. Epub 2004/11/04. DOI: 10.1139/y04-057.

Ring H. and Rosenthal N. Controlled study of neuroprosthetic functional electrical stimulation in sub-acute post-stroke rehabilitation. J Rehabil Med. 2005;37(1):32-36. Epub 2005/03/25. DOI: 10.1080/16501970410035387.

Shindo K., Fujiwara T., Hara J., Oba H., Hotta F., Tsuji T., et al. Effectiveness of hybrid assistive neuromuscular dynamic stimulation therapy in patients with subacute stroke: a randomized controlled pilot trial. Neurorehabil Neural Repair. 2011;25(9):830-837. Epub 2011/06/15. DOI: 10.1177/1545968311408917.

Tarkka I. M., Pitkänen K., Popovic D. B., Vanninen R. and Könönen M. Functional electrical therapy for hemiparesis alleviates disability and enhances neuroplasticity. Tohoku J Exp Med. 2011;225(1):71-76. Epub 2011/09/01. DOI: 10.1620/tjem.225.71.

Thrasher T. A., Zivanovic V., McIlroy W. and Popovic M. R. Rehabilitation of reaching and grasping function in severe hemiplegic patients using functional electrical stimulation therapy. Neurorehabil Neural Repair. 2008;22(6):706-714. Epub 2008/10/31. DOI: 10.1177/1545968308317436.

Explanations: +/- significant effects for/against the former additional intervention, Ø no significant group differences ND = no statistical data available or reported (for group comparison)

Abbrevations: 10-CMT – Ten-Cup-Moving Test; 9-HPT – Nine-Hole-Peg Test; Active ROM – Active range of motion; ADL – activities of daily living; AE – adverse event; AL – Activity limitations; ARAT – Action Research Arm Test; BBT – Box and Block Test; BF – Body function and structure; CG – control group; CMSA – Chedoke McMaster Stroke Assessment; CMSMR – Chedoke McMaster Stages of Motor Recovery; EBI – Extended Barthel Index; FIM – Functional Independence measure; FMA – Fugl Meyer Assessment; FTHUE – Functional Test for the Hemiplegic Upper Extremity; FU – Follow-up; IG – intervention group; JTHFT – Jebsen Taylor Hand Function Test; M – Month; MAL – Motor Activity Log Scale; MAS – Modified Ashworth Scale; MBI – Modified Barthel Index; MS – Muscle Strength; PI – Post-intervention; QoL – Quality of Life; RELHFT – Rehabilitation Engineering Laboratory Hand Function Test; S – Shoulder; SA – Self-Assessment; SAE – Serious adverse event; SF – Shoulder flexion; SIAS – Stroke Impairment Assessment Set; SoC – Standard rehabilitation; UEFT – Upper Extremity Function Test; W – Week; W+F – Wrist and Finger; WE – Wrist extension; WF – Wrist flexion; WMFT – Wolf Motor Function test.

[53] IG improved significantly more than the CG in terms of object manipulation, palmar grip torque, and pinch grip pulling force

[54] No significant differences in blocks score and eccentric load

5 Discussion

In this assessment, we evaluated whether the use of robotics or functional electrical stimulation (FES) yield clinical benefits in post-stroke rehabilitation. For this purpose, we have conducted an update systematic review collaboratively with the ReMoS working group for lower limb stroke rehabilitation. Additionally, we summarised the evidence synthesis for these two interventions in upper limb stroke rehabilitation from a recent AWMF S3 guideline [4].

RAR und FES: Update SR bei unteren Extremitäten; Zusammenfassung der Evidenz aus LL bei oberen Extremitäten

5.1 Summary and Interpretation

For robot assisted stroke rehabilitation (RAR) of lower limbs, we found 11 RCTs. The evidence indicates that some types of RAR (especially end-effector based gait training) may be beneficial for stroke rehabilitation for patients in the subacute stadium, dependant on their clinical deficit. Overall, the strength of the comparative evidence ranged from low (mobile exoskeletons) to moderate (stationary exoskeletons, stationary end-effectors).

RAR untere Extremitäten: Evidenz deutet auf Zusatznutzen v. a. von End-Effektoren hin

For FES stroke rehabilitation of lower limbs, the evidence consisted of 17 RCTs (LoE: 1b). The evidence was insufficient to prove that any of the FES interventions and standard rehabilitation was superior to standard rehabilitation alone, although the evidence suggests that the tilt sensor FES systems are non-inferior when compared to AFO in patients with drop foot. The strength of comparative evidence was *very low* (FES combined with electromechanical gait trainer, bike training (cycling) with FES, mixed electrostimulation programs and multi-channel FES with percutaneous wire electrodes) *low* (gait training with flexor reflex surface stimulation, multi-channel surface FES, electrostimulation of the peroneal nerve while walking with implanted system and treadmill training with FES) and *moderate* (tilt sensor surface FES, and N. peroneus surface FES).

FES unteren Extremitäten: unzureichende Evidenz für Zusatznutzen von FES zur Standard-Rehabiliation

For upper limb stroke rehabilitation, the AWMF S3 guideline [4] found evidence consisting of 16 RCTs (LoE: 1b) for RAR and 9 RCTs (LoE: 1b) for FES that fulfilled our inclusion criteria. The evidence identified by the guideline supports arm robot therapies including both exoskeletons and other electromechanical active robotic devices especially for patients in the subacute stadium. For FES, the AWMF S3 guideline [4] found *low* quality evidence demonstrating that FES, indicated for patients with severe incomplete hand paresis and partially preserved proximal motoric function (movement and holding function), can be used for inducing grasping and releasing or finger and hand extension combined with training of everyday activities. This applies in particular if the treatment aims to improve selective mobility or arm activities and patients are willing to train one to two hours with FES. Further *low* quality evidence suggests that FES can also be considered for shoulder and elbow movements.

RAR oberen Extremitäten: Evidenz für Zusatznutzen

FES oberen Extremitäten: unzureichende Evidenz

Einbettung in bestehendes Wissen:

The results identified in this review are somewhat aligned with other recent systematic reviews:

Review aus 2018 zu RAR und FES unteren Extremitäten: „mixed evidence"

For lower limb rehabilitation, a recent systematic review of the Evidence-Based Review of Stroke Rehabilitation (EBRSR) [1] included 35 RCTs in 2018 evaluating the clinical benefit of FES and found that FES may be beneficial to improve gait, yet stating that the literature is rather mixed for FES more broadly (alone or in combination with other interventions). The clinical benefit of using robot assisted lower limb rehabilitation was assessed in the same review: the EBRSR review [1] found 32 RCTs in 2018 evaluating the clinical benefit of lower limb robotics for motor rehabilitation. The evidence was found to be mixed regarding the effectiveness of end-effectors, and exoskeleton systems. Further, the review authors found portable exoskeletons and robotic arm control systems likely to be not effective for lower limb rehabilitation. Lokomat training, however, was judged to be potentially beneficial for lower limb rehabilitation following stroke.

Cochrane Review aus 2017: Evidenz deutet auf Nutzen von RAR untere Extremitäten hin

In 2017, a Cochrane review [6] included 36 RCTs and concluded more broadly that post-stroke patients receiving electromechanical-assisted gait training compared with physiotherapy are more likely to achieve the goal to independently walking when compared to patients who do not use these rehabilitation devices. More specifically, patients in the first three months after stroke appear to benefit most from this type of intervention. The review further found that these devices did not increase the risk of participants drop out from any cause, with an odds-ratio of 0.67 (95%CI: 0.43-1.05; p=0.08). However, the review also found sparse reporting on adverse events as such in the included trials. The review authors further noted that role of the type of device is still not clear.

Review aus 2018 zu RAR & FES obere Extremitäten: „mixed evidence"

For upper limb stroke rehabilitation, a recent systematic review of the EBRSR [2] included 67 RCTs in 2018, evaluating various forms of electrical stimulation: the review authors found the literature to be mixed regrading cyclic and EMG-triggered neuromuscular electrical stimulation types, as well as functional electrical stimulation, alone or combined with other therapy approaches. Further, the authors noted that the subtypes of (neuromuscular) electrical stimulation may not be more beneficial compared to each other. Based on 54 RCTs evaluating upper limb robotics for motor rehabilitation, the EBRSR concluded in 2018 that the evidence is mixed with regard to arm/shoulder end-effector or exoskeleton robotics for upper limb stroke rehabilitation.

Diskrepanz zu LL Ergebnisse

This interpretation of the evidence with regard to robotic devices for upper limb stroke rehabilitation is not fully in agreement with the one to be found in the AWMF S3 guideline [4] that we summarised in this HTA report.

Cochrane Bericht aus 2018 kommt zu hoher Qualität der Evidenz f. Nutzen von RAR oberen Extremitäten

Autoren betonen Heterogenität der Studien

On the contrary and aligned with the interpretation of the AWMF S3 guideline, a Cochrane review [78] included 45 RCTs in 2018 and concluded there is high quality evidence of a small benefit from robotic arm-training with regard to activities of daily living, arm function, and arm muscle strength. The quality of the evidence was rated to be high, but the authors noted that heterogeneity exists, among others, with regard to the amount of training, type of treatment, participant characteristics. The review authors further noted that role of the type of device is still not clear. With regard to safety of the devices, the review found AEs occurring rarely being not related to the therapy [78].

Complementary to this review, network meta-analysis [153] was published in 2020 that analysed six broad categories of 28 different robotic devices for upper limb stroke rehabilitation. Based on 55 RCTs the authors found evidence that no one category or robotic device may be better or worse than any other device category. Hence, it is concluded that the type of device (e.g., exoskeleton, end-effector, distal, unilateral) may not be affecting patient outcomes and that outcomes of robot assisted training were comparable to conventional therapy. It is to be noted that network-meta analyses are indirect comparisons and heterogeneity between studies existed.

Netzwerk Meta-Analyse fand keinen Unterschied zwischen Exoskeletten und End-Effektoren bei oberen Extremitäten Rehabilitation, aber: nur indirekter Vergleich

Further, a recent randomised controlled trial (RATULS; n=770; arguably the most robust trial available for robotic arm training) that was also included in the evidence synthesis by the AWMF S3 guideline [4] showed that robot-assisted training in comparison to usual care did not improve upper limb function after stroke. They concluded that the results do not support the use of robot-assisted training for upper limb rehabilitation following stroke [154]. Despite some secondary outcome analysis favouring higher dose robot-assisted training, the effects were small and the cost-utility analysis found higher costs for robot- assisted training in comparison to usual care, with £5387 and £3785 per participant respectively [154, 155]. These results and conclusions are in stark contrast to the ones from the Cochrane review [155] and the AWMF S3 guideline [4], although the latter also included the RATULS trial in their review. The difference may be explained by the fact that variations exist in treatment (e.g., intensity, duration and type of training) of the pooled meta-analysis from the Cochrane review, on the one hand, and that the time to start of training after stroke was not considered and the target group and the ideal type of robot-assisted training may, in general, not be refined at this moment in time [155]. Further, the RATULS trial included both subacute and chronic stroke patients and the positive conclusion from the AWMF S3 guideline [4] was primarily applicable for patients in the subacute stadium of stroke.

rezentes RCT (n=770) fand keinen Unterschied der RAR bei oberen Extremitäten zu Standardrehabilitation hinsichtlich der Funktionalität

RCT schloss sowohl subakute als auch chronische Schlaganfall-Patient*innen ein

Unterschiede durch Intensität, Dauer, Typ des Trainings, aber auch Trainingsbeginn und Schweregrad zu erklären

In this context, it is to be noted that there are currently numerous robotic devices available that have also slightly different technical characteristics as also seen in this HTA report. In a letter to the editor, it is highlighted that the RATULS trial shows that large, well conducted, multisite trials that use only one of these devices is possible: "getting the fundamentals right for future trials is imperative to advance the field" [155]. However, the lack of refining the intervention coupled with an open door to new approvals through the 501 (k) FDA loophole may be further counterproductive in generating solid generalizable evidence.

viele Geräte derzeit verfügbar

The heterogeneity with regard to the different robotic devices is to be regarded as a limitation of our review, the aforementioned reviews and the clinical evaluation of the intervention more broadly: most of the devices were cleared by the FDA under the 510 (k) clearance, meaning that they are considered "equivalent" without full new evaluation. As a result, numerous medical devices are currently available for the interventions under investigation. This could open the door for some marketed devices labelled as exoskeleton or end-effector with even more uncertainty with regard to the comparative effectiveness (and safety).

Heterogenität hinsichtlich technischen Charakteristika, Kosten (Wirksamkeit?)

potentieller Nutzen bei Nicht-Unterlegenheit kombiniert mit Entlastung der Physiotherapeut*innen (Zeit, körperliche Anstrengung, etc);

gesundheits-ökonomische Evaluierungen sinnvoll

Further, there are not only technological differences between these devices, but also related to costs. If, for instance, a course of action with FES or robot assisted rehabilitation is not clearly superior to standard rehabilitation, but non-inferior while replacing efforts of the physiotherapist (in the context of robotic devices) or an ankle-foot-orthosis (in the context of FES), the course with one of these interventions may still be worthwhile, if the overall cost of the course of action is lower than the standard rehabilitation pathway. While the RATULS trial [154] showed that a care pathway with robotic devices for upper limb stroke rehabilitation was clearly found to be more costly than conventional rehabilitation, it is hard to generalise these results for all robotic devices. Hence, full economic evaluations are needed to shed more light on the overall benefit of these interventions in stroke rehabilitation.

5.2 Ongoing studies

viele laufende Studien mit kleinem Sample
24 RCT zu RAR: nur 2 > 100 Pts
Ergebnisse 2022/23

There are currently numerous ongoing studies evaluating the benefit of RAR or FES for stroke rehabilitation. We have identified 24 RCTs for robot assisted rehabilitation and some further six RCTs for FES. For RAR, the studies appear to be mostly proof-of-concept RCTs evaluating new robotics in a small patient sample. There are currently only two ongoing RCTs with more than 100 enrolled patients evaluating a robotic device in comparison to standard rehabilitation: one RCT (n=150) evaluates the G-EO system for lower limb stroke rehabilitation in elderly patients. The second ongoing study (n=132) evaluates the robotic exoskeleton called "KINARM" in different stages and intensities for upper limb stroke rehabilitation. The estimated primary completion date is September 2022 and October 2023 respectively.

6 RCT zu FES: nur 1 > 100 Pts
Ergebnisse 2019 ?

For FES, we have identified six ongoing RCTs, yet five of these six RCTs enrolled less than 100 patients. The study with more than 100 enrolled patients ("RALLY") evaluates the therapeutic effect of peroneal nerve stimulation for lower extremity in patients with sub-acute post-stroke patients. The estimated primary completion date of this trial has already passed (in 2019). There are no published manuscripts indexed for the RALLY study.

More information on the identified ongoing studies can be found in Table A-9 (for RAR) and Table A-10 (for FES) respectively.

5.3 Limitations

Limitationen: Evaluierung der Sicherheit limitiert durch fehlendes Reporting der Studien; kein MCID definiert, aber starke Einbindung von Kliniker*innen

Every systematic review needs to be reflected in light of its limitations:

- The evaluation of the safety of robotic devices and FES was limited by the fact that the primary studies often failed to report on safety outcomes.
- We did not consider 2b LoE RCTs and observational studies. In the latter, rare adverse events could, in theory, be better detectable in comparison to RCTs. Observational studies are, however, more prone to internal validity concerns and the reporting standards also in respect to adverse events are usually worse in comparison to the one to be found in RCTs.

- There were numerous different outcome instruments used to evaluate one outcome of interest in primary studies. In addition, some of the selected outcomes overlapped. As a result, this terminological issue resulted in both difficulties to differentiate clearly between outcomes of interest and to cluster the specific outcome instruments to the specific outcomes. This could, in future, be resolved by standardising the measurement of recovery in stroke trials [77] and adhering to these standards.
- Further, we only cursorily considered the specific stadium of stroke in this HTA report due to the rather broad research question and the target audience of this report. We did consider the stadium of the stroke in the drawn conclusion and the reader is referred to the guideline we cooperated with for a more nuanced description of the evidence reflecting stroke chronicity more detailed.
- A further limitation of our review is that we only reported whether differences were statistically significant favouring/not favouring an intervention of interest. A pre-defined minimal clinically important difference (MCID) could have helped to further evaluate whether these differences are actually meaningful in a clinical context.
- Last but not least, the use of aggregated data, like in systematic reviews or guidelines, or the evaluation of a large number of clinical studies with very different medical devices always implies a loss of more detailed qualitative information that might be explanatory in the interpretation of the findings. The information lost are details on intensity, duration and type of training, eventual effects in subpopulations.

However our evidence synthesis was conducted in close cooperation with clinical experts as part of the guideline working group and hence, our conclusions of the evidence do reflect the importance of the detected difference.

6 Conclusion

Evidenz deutet auf Nutzen der RAR hin, aber hohe Kosten, Heterogenität der Int.

The identified evidence indicates that robotic assisted rehabilitation (both exoskeletons and end-effectors) for stroke rehabilitation may yield a clinical benefit in upper limb rehabilitation in the subacute stadium of stroke, dependant on their clinical deficit. For lower limb stroke rehabilitation, the evidence is less robust. The evidence favouring robotic assisted rehabilitation is, however, weakened by uncertainties with regard to the role of the specific robotic device and high costs of some devices.

FES: unzureichende Evidenz; manche Arten der FES nicht-unterlegen (AFO)

For functional electrical stimulation, there is currently insufficient evidence indicating that FES as an add-on measure is superior to standard rehabilitation alone in upper or lower limb stroke rehabilitation. Some of the FES devices were, however, proven non-inferior to AFO in patients with drop foot.

gesundheitsökonomische Evaluierungen notwendig

In light of numerous therapeutic options available in stroke rehabilitation, often with limited proven benefit, but increased costs, health economic evaluations for these interventions that showed a certain clinical benefit or at least non-inferiority is recommended. Here, the focus should be on relieving the physiotherapist's workload (both in terms of time and physical). For such an evaluation, it is essential to consider the general conditions or the organizational setting and the severity of the stroke. On the other hand, a disinvestment in treatment modalities that are not proven by evidence or are not cost-effective should be considered.

7 References

[1] Iruthayarajah J., Iliescu A., Foley N., Mirkowski M., Saikaley M., Weiner J., et al. Lower Extremity Motor Reahbilitation Interventions. Evidence Review. [updated 01.03.2018; cited 18.09.2020]. Available from: http://www.ebrsr.com/sites/default/files/chapter%209_Jan22_v19.pdf.

[2] Iruthayarajah J., Mirkowski M., Foley N., Iliescu A., Caughlin S., Fragis N., et al. Upper Extremity Motor Rehabilitation Interventions. Evidence Review. [updated 01.03.2018; cited 18.09.2020]. Available from: http://www.ebrsr.com/sites/default/files/chapter%2010_version%2019.pdf.

[3] Molteni F., Gasperini G., Cannaviello G. and Guanziroli E. Exoskeleton and End-Effector Robots for Upper and Lower Limbs Rehabilitation: Narrative Review. Pm r. 2018;10(9 Suppl 2):S174-s188. Epub 2018/10/03. DOI: 10.1016/j.pmrj.2018.06.005.

[4] Platz T., et al.,. Rehabilitative Therapie bei Armparese nach Schlaganfall. Deutschen Gesellschaft für NeuroRehabilitation (DGNR), 2020 [cited 26.08.2020]. Available from: https://www.awmf.org/uploads/tx_szleitlinien/080-001l_S3_Rehabilitative_Therapie_bei_Armparese_nach_Schlaganfall_2020-07.pdf.

[5] Exoskeleton Report. G-EO System. [cited 03.07.2020]. Available from: https://exoskeletonreport.com/product/g-eo-system/.

[6] Carrera I., Moreno H. A., Sierra S., Campos A., Munera M. and Cifuentes C. A. Technologies for Therapy and Assistance of Lower Limb Disabilities: Sit to Stand and Walking. In: Cardona M., Saolanki V. K. and Garcia Cena C. E., editors. Exoskeleton Robots for Rehabilitation and Healthcare Devices. Singapore: Springer; 2020.

[7] Reha Stim Medtec AG. Gangtrainer GT II. [cited 15.08.2020]. Available from: https://www.teida.lt/out/media/Gait_Trainer_GTI_Flyers_Englisch_2013.pdf.

[8] Exoskeleton Report. Walkbot. [cited 20.08.2020]. Available from: https://exoskeletonreport.com/product/walkbot/.

[9] Peshkin M., Brown D., Santos-Munne J. J., Makhlin A., Lewis E., Colgate J., et al. KineAssist: A robotic overground gait and balance training device2005. 241-246 p.

[10] Nakanishi Y., Wada F., Saeki S. and Hachisuka K. Rapid changes in arousal states of healthy volunteers during robot-assisted gait training: a quantitative time-series electroencephalography study. Journal of neuroengineering and rehabilitation. 2014;11:59-59. DOI: 10.1186/1743-0003-11-59.

[11] Food and Drug Administration (FDA). Honda Walking Assist Device. FDA clearance. 2018 [cited 20.08.2020]. Available from: https://www.accessdata.fda.gov/cdrh_docs/pdf18/K181294.pdf.

[12] ACN Newswire. Honda Walking Assist Obtains Medical Device Approval in the EU. 2018 [cited 20.08.2020]. Available from: http://en.acnnewswire.com/press-release/english/40944/honda-walking-assist-obtains-medical-device-approval-in-the-eu.

[13] Exoskeleton Report. Walking Assist. [cited 20.07.2020]. Available from: https://exoskeletonreport.com/product/honda-walking-assist/.

[14] Stein J., Bishop L., Stein D. J. and Wong C. K. Gait training with a robotic leg brace after stroke: a randomized controlled pilot study. Am J Phys Med Rehabil. 2014;93(11):987-994. Epub 2014/06/06. DOI: 10.1097/phm.0000000000000119.

[15] ReWalk Robotics Ltd. ReStore Soft Exo-Suit – Eine Revolution für das Gangtraining von Schlaganfallpatienten. [cited 20.08.2020]. Available from: https://rewalk.com/de/restore-exo-suit/.

[16] Exoskeleton Report. Indego Cleared By FDA For Clinical And Personal Use. [cited 15.08.2020]. Available from: https://exoskeletonreport.com/2016/03/indego-cleared-fda-clinical-personal-use/.

[17] Parker Hannifin Corp. Introduction to Indego Therapy. [cited 20.08.2020]. Available from: http://www.indego.com/indego/us/en/indego-therapy.

[18] ExoAtlet. ExoAtlet II. [cited 15.10.2020]. Available from: https://exoatlet.lu/product-page-exoatlet-ii/#.

[19] Exoskeleton Report. ExoAtlet II. [cited 15.10.2020]. Available from: https://exoskeletonreport.com/product/exoatlet-ii/.

[20] Forrester L. W., Roy A., Goodman R. N., Rietschel J., Barton J. E., Krebs H. I., et al. Clinical application of a modular ankle robot for stroke rehabilitation. NeuroRehabilitation. 2013;33(1):85-97. DOI: 10.3233/NRE-130931.

[21] Klamroth-Marganska V., Blanco J., Campen K., Curt A., Dietz V., Ettlin T., et al. Three-dimensional, task-specific robot therapy of the arm after stroke: a multicentre, parallel-group randomised trial. Lancet Neurol. 2014;13(2):159-166. Epub 2014/01/03. DOI: 10.1016/s1474-4422(13)70305-3.

[22] Nef T., Guidali M. and Riener R. ARMin III – arm therapy exoskeleton with an ergonomic shoulder actuation. Applied Bionics and Biomechanics. 2009;6:127-142. DOI: 10.1080/11762320902840179.

[23] Masiero S., Armani M. and Rosati G. Upper-limb robot-assisted therapy in rehabilitation of acute stroke patients: focused review and results of new randomized controlled trial. J Rehabil Res Dev. 2011;48(4):355-366. Epub 2011/06/16. DOI: 10.1682/jrrd.2010.04.0063.

[24] Bionik. InMotionArm. [cited 20.08.2020]. Available from: https://www.bioniklabs.com/products/inmotion-arm.

[25] Exoskeleton Report. InMotion ARM [cited 21.09.2020]. Available from: https://exoskeletonreport.com/product/inmotion-arm/.

[26] Wolbrecht E. T., Chan V., Reinkensmeyer D. J. and Bobrow J. E. Optimizing compliant, model-based robotic assistance to promote neurorehabilitation. IEEE Trans Neural Syst Rehabil Eng. 2008;16(3):286-297. Epub 2008/07/01. DOI: 10.1109/tnsre.2008.918389.

[27] Coote S., Murphy B., Harwin W. and Stokes E. The effect of the GENTLE/s robot-mediated therapy system on arm function after stroke. Clin Rehabil. 2008;22(5):395-405. Epub 2008/04/29. DOI: 10.1177/0269215507085060.

[28] Tomić T. J. D., Savić A. M., Vidaković A. S., Rodić S. Z., Isaković M. S., Rodríguez-de-Pablo C., et al. ArmAssist Robotic System versus Matched Conventional Therapy for Poststroke Upper Limb Rehabilitation: A Randomized Clinical Trial. BioMed research international. 2017;2017:7659893-7659893. Epub 2017/01/31. DOI: 10.1155/2017/7659893.

[29] Kahn L. E., Zygman M. L., Rymer W. Z. and Reinkensmeyer D. J. Robot-assisted reaching exercise promotes arm movement recovery in chronic hemiparetic stroke: a randomized controlled pilot study. Journal of neuroengineering and rehabilitation. 2006;3:12-12. DOI: 10.1186/1743-0003-3-12.

[30] Sicuri C., Porcellini G. and Merolla G. Robotics in shoulder rehabilitation. Muscles Ligaments Tendons J. 2014;4(2):207-213. Epub 2014/10/22.

[31] FDA report. Armeo 26405. [cited 01.08.2020]. Available from: https://fda.report/GUDID/07640174660001.

[32] Hocoma. Armeo (R) Power. [cited 21.08.2020]. Available from: https://www.hocoma.com/us/solutions/armeo-power/.

[33] Exoskeleton Report. ReoGo. [cited 15.08.2020]. Available from: https://exoskeletonreport.com/product/reogo/.

[34] Byl N. N., Abrams G. M., Pitsch E., Fedulow I., Kim H., Simkins M., et al. Chronic stroke survivors achieve comparable outcomes following virtual task specific repetitive training guided by a wearable robotic orthosis (UL-EXO7) and actual task specific repetitive training guided by a physical therapist. J Hand Ther. 2013;26(4):343-352; quiz 352. Epub 2013/08/06. DOI: 10.1016/j.jht.2013.06.001.

[35] Gillen G. Rehabilitation Technologies to Promote Upper Limb Recovery after Strok. In: Gillen G., editor. Stroke Rehabilitation A Function-Based Approach. Missouri: Elsevier. p. 486-511.

[36] Connelly L., Jia Y., Toro M. L., Stoykov M. E., Kenyon R. V. and Kamper D. G. A pneumatic glove and immersive virtual reality environment for hand rehabilitative training after stroke. IEEE Trans Neural Syst Rehabil Eng. 2010;18(5):551-559. Epub 2010/04/10. DOI: 10.1109/tnsre.2010.2047588.

[37] Dohle C., Tholen R., Wittenberg H., Quintern J., Saal S. and Stephan K. M. [Evidence-based rehabilitation of mobility after stroke]. Nervenarzt. 2016;87(10):1062-1067. Epub 2016/08/18. Evidenzbasierte Rehabilitation der Mobilität nach Schlaganfall. DOI: 10.1007/s00115-016-0188-8.

[38] Marquez-Chin C. and Popovic M. R. Functional electrical stimulation therapy for restoration of motor function after spinal cord injury and stroke: a review. Biomedical engineering online. 2020;19(1):34-34. DOI: 10.1186/s12938-020-00773-4.

[39] Oddstock Medical Ltd. ODFS® Pace Kit. [cited 20.08.2020]. Available from: https://www.odstockmedical.com/products/odfs%C2%AE-pace-kit.

[40] Corp. A. Walkaide (R) II. [cited 20.08.2020]. Available from: https://acplus.com/walkaide/.

[41] Bioness Inc. Walk More Naturally with Speed, Stability and Confidence. [cited 15.08.2020]. Available from: https://www.bioness.com/Products/L300_for_Foot_Drop.php.

[42] Odstock Medical Ltd. STIMuSTEP (implanted) [cited 21.09.2020]. Available from: https://www.odstockmedical.com/category/knowledge-base/equipment/stimustep-implanted.

[43] Hasomed GmbH. RehaMove – Motion Training with Functional Electrical Stimulation (FES). [cited 20.08.2020]. Available from: https://hasomed.de/en/products/rehamove/.

[44] Food and Drug Administration (FDA). MyGait Stimulation System. 510(k) premarket notification. 2015 [cited 21.09.2020]. Available from: https://www.accessdata.fda.gov/cdrh_docs/pdf14/K141812.pdf.

[45] Bioness Inc. Das H200 Hand-Rehabilitationssystem. [cited 20.08.2020]. Available from: https://www.bioness.com/Deutschland/H200_Wireless__bei_Handl%C3%A4hmungen.php.

[46] Hara Y., Ogawa S., Tsujiuchi K. and Muraoka Y. A home-based rehabilitation program for the hemiplegic upper extremity by power-assisted functional electrical stimulation. Disabil Rehabil. 2008;30:296-304. DOI: 10.1080/09638280701265539.

[47] Shindo K., Fujiwara T., Hara J., Oba H., Hotta F., Tsuji T., et al. Effectiveness of hybrid assistive neuromuscular dynamic stimulation therapy in patients with subacute stroke: a randomized controlled pilot trial. Neurorehabil Neural Repair. 2011;25(9):830-837. Epub 2011/06/15. DOI: 10.1177/1545968311408917.

[48] Popovic M., Masani K. and MMicera S. Functional Electrical Stimulation Therapy: Recovery of Function Following Spinal Cord Injury and Stroke. In: Dietz V., Nef T. and Zev Rymer W., editors. Neurorehabilitation Technology. London: Springer; 2012.

[49] Hesse S., Schmidt H., Werner C. and Bardeleben A. Upper and lower extremity robotic devices for rehabilitation and for studying motor control. Curr Opin Neurol. 2003;16(6):705-710. Epub 2003/11/19. DOI: 10.1097/01.wco.0000102630.16692.38.

[50] Louie D. R. and Eng J. J. Powered robotic exoskeletons in post-stroke rehabilitation of gait: a scoping review. Journal of neuroengineering and rehabilitation. 2016;13(1):53-53. DOI: 10.1186/s12984-016-0162-5.

[51] Lynch C. and Popovic M. Functional Electrical Stimulation. Control Systems, IEEE. 2008;28:40-50. DOI: 10.1109/MCS.2007.914689.

[52] Food and Drug Administration (FDA). 882.5810 External functional neuromuscular stimulator. [cited 10.08.2020]. Available from: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=882.5810.

[53] Food and Drug Administration (FDA). Powered exoskeleton. [cited 10.08.2020]. Available from: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPCD/classification.cfm?ID=PHL.

[54] Weber L. M. and Stein J. The use of robots in stroke rehabilitation: A narrative review. NeuroRehabilitation. 2018;43:99-110. DOI: 10.3233/NRE-172408.

[55] Deximed. Rehabilitation nach dem Schlaganfall [updated 04.11.2019 cited 15.08.2020]. Available from: https://deximed.de/home/b/herz-gefaesse-kreislauf/patienteninformationen/schlaganfall/schlaganfall-rehabilitation/.

[56] Harris J. E. and Eng J. J. Goal Priorities Identified through Client-Centred Measurement in Individuals with Chronic Stroke. Physiotherapy Canada Physiotherapie Canada. 2004;56(3):171-176. DOI: 10.2310/6640.2004.00017.

[57] Conrad N., Doering B., Rief W. and Exner C. Looking beyond the importance of life goals. The personal goal model of subjective well-being in neuropsychological rehabilitation. Clin Rehabil. 2010;24:431-443. DOI: 10.1177/0269215509358930.

[58] DynaMed. Record No. T143427, Stroke (Acute Management). [updated 2018; cited 14.09.2020]. Available from: https://www.dynamed.com/topics/dmp~AN~T143427.

[59] Bernhardt J., Hayward K. S., Kwakkel G., Ward N. S., Wolf S. L., Borschmann K., et al. Agreed Definitions and a Shared Vision for New Standards in Stroke Recovery Research: The Stroke Recovery and Rehabilitation Roundtable Taskforce. Neurorehabil Neural Repair. 2017;31(9):793-799. Epub 2017/09/25. DOI: 10.1177/1545968317732668.

[60] American Stroke Association. Hemiparesis. [updated 06.04.2019; cited 15.08.2020]. Available from: https://www.stroke.org/en/about-stroke/effects-of-stroke/physical-effects-of-stroke/physical-impact/hemiparesis.

[61] Association A. S. Foot Drop. [cited 23.10.2020]. Available from: https://www.stroke.org/en/about-stroke/effects-of-stroke/physical-effects-of-stroke/physical-impact/foot-drop.

[62] National Institute for Heart Lung and Blood Institute (NIHLBI). Stroke. [cited 01.08.2020]. Available from: https://www.nhlbi.nih.gov/health-topics/stroke.

[63] Kwakkel G. Impact of intensity of practice after stroke: issues for consideration. Disabil Rehabil. 2006;28(13-14):823-830. Epub 2006/06/17. DOI: 10.1080/09638280500534861.

[64] Kwakkel G. and Kollen B. J. Predicting activities after stroke: what is clinically relevant? Int J Stroke. 2013;8(1):25-32. Epub 2013/01/03. DOI: 10.1111/j.1747-4949.2012.00967.x.

[65] Edwardson M. Ischemic stroke prognosis in adults. [updated 01.08.2020; cited 15.08.2020]. Available from: https://www.uptodate.com/contents/ischemic-stroke-prognosis-in-adults?search=hemiparesis%20stroke&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1.

[66] Veerbeek J. M., Van Wegen E. E., Harmeling-Van der Wel B. C. and Kwakkel G. Is accurate prediction of gait in nonambulatory stroke patients possible within 72 hours poststroke? The EPOS study. Neurorehabil Neural Repair. 2011;25(3):268-274. Epub 2010/12/28. DOI: 10.1177/1545968310384271.

[67] Österreichische Schlaganfallgesellschaft (ÖGSF). Zahlen und Fakten. [cited 23.10.2020]. Available from: https://www.ögsf.at/stroke-units/zahlen-und-fakten/.

[68] GBD 2016 Stroke Collaborators. Global, regional, and national burden of stroke, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol. 2019;18(5):439-458. Epub 2019/03/16. DOI: 10.1016/s1474-4422(19)30034-1.

[69] American Stroke Association. Common Diagnosis Methods. [cited 01.08.2020]. Available from: https://www.stroke.org/en/about-stroke/treatment/common-diagnosis-methods.

[70] NHS United Kingdom. Foot drop. [cited 15.09.2020]. Available from: https://www.nhs.uk/conditions/foot-drop/.

[71] Platz T. Evidenzbasierte Armrehabilitation nach Schlaganfall – ein Überblick. neuroreha. 2020;12(02):58-62. DOI: 10.1055/a-1156-3752.

[72] Winstein C. J., Stein J., Arena R., Bates B., Cherney L. R., Cramer S. C., et al. Guidelines for Adult Stroke Rehabilitation and Recovery: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke. 2016;47(6):e98-e169. Epub 2016/05/06. DOI: 10.1161/str.0000000000000098.

[73] Nelles et al. Rehabilitation von sensomotorischen Störungen (S2k-Leitlinie). 2018 [cited 15.08.2020]. Available from: https://www.awmf.org/uploads/tx_szleitlinien/030-123l_S2k_Rehabilitation_sensomotorische_St%C3%B6rungen_2018-04-verlaengert.pdf.

[74] Liberati A., Altman D. G., Tetzlaff J., Mulrow C., Gøtzsche P. C., Ioannidis J. P. A., et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. J Clin Epidemiol. 2009;62(10):e1-e34. DOI: https://doi.org/10.1016/j.jclinepi.2009.06.006.

[75] Moher D., Liberati A., Tetzlaff J. and Altman D. G. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. International Journal of Surgery. 2010;8(5):336-341. DOI: https://doi.org/10.1016/j.ijsu.2010.02.007.

[76] EUnetHTA. Methodology Guidelines. 2015 [cited 01.02.2019]. Available from: https://www.eunethta.eu/methodology-guidelines/.

[77] Kwakkel G., Lannin N. A., Borschmann K., English C., Ali M., Churilov L., et al. Standardized measurement of sensorimotor recovery in stroke trials: Consensus-based core recommendations from the Stroke Recovery and Rehabilitation Roundtable. Int J Stroke. 2017;12(5):451-461. Epub 2017/07/13. DOI: 10.1177/1747493017711813.

[78] Mehrholz J., Pohl M., Platz T., Kugler J. and Elsner B. Electromechanical and robot-assisted arm training for improving activities of daily living, arm function, and arm muscle strength after stroke. 2018 [cited 21.09.2020]. Available from: http://dx.doi.org/10.1002/14651858.CD006876.pub5.

[79] Mehrholz J., Thomas S., Werner C., Kugler J., Pohl M. and Elsner B. Electromechanical-assisted training for walking after stroke. Cochrane Database of Systematic Reviews. 2017(5). DOI: 10.1002/14651858.CD006185.pub4.

[80] Eraifej J., Clark W., France B., Desando S. and Moore D. Effectiveness of upper limb functional electrical stimulation after stroke for the improvement of activities of daily living and motor function: a systematic review and meta-analysis. Syst Rev. 2017;6(1):40. Epub 2017/03/02. DOI: 10.1186/s13643-017-0435-5.

[81] Maher C. G., Sherrington C., Herbert R. D., Moseley A. M. and Elkins M. Reliability of the PEDro scale for rating quality of randomized controlled trials. Phys Ther. 2003;83(8):713-721. Epub 2003/07/29.

[82] Brouwers M. C., Kerkvliet K., Spithoff K. and Consortium A. N. S. The AGREE Reporting Checklist: a tool to improve reporting of clinical practice guidelines. BMJ (Clinical research ed). 2016;352:i1152-i1152. DOI: 10.1136/bmj.i1152.

[83] The Centre for Evidence-Based Medicine. Oxford Centre for Evidence-based Medicine – Levels of Evidence. 2009 [cited 03.09.2020]. Available from: https://www.cebm.net/2009/06/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/.

[84] Guyatt G., Oxman A. D., Akl E. A., Kunz R., Vist G., Brozek J., et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol. 2011;64(4):383-394. Epub 2011/01/05. DOI: 10.1016/j.jclinepi.2010.04.026.

[85] Shirley Ryan AbilityLab. Functional Ambulation Category. [cited 15.08.2020]. Available from: https://www.sralab.org/rehabilitation-measures/functional-ambulation-category.

[86] Shirley Ryan AbilityLab. Chedoke-McMaster Stroke Assessment Measure. Available from: https://www.sralab.org/rehabilitation-measures/chedoke-mcmaster-stroke-assessment-measure.

[87] Shirley Ryan AbilityLab. Clinical Outcome Variable Scale. Available from: https://www.sralab.org/rehabilitation-measures/clinical-outcome-variables-scale.

[88] Shirley Ryan AbilityLab. Rivermead Mobility Index. [cited 15.08.2020]. Available from: https://www.sralab.org/rehabilitation-measures/rivermead-mobility-index.

[89] Shirley Ryan AbilityLab. Berg Balance Scale. [cited 15.06.2020]. Available from: https://www.sralab.org/rehabilitation-measures/berg-balance-scale.

[90] Physiopedia. Timed Up and Go Test. [cited 15.07.2020]. Available from: https://www.physio-pedia.com/Timed_Up_and_Go_Test_(TUG).

[91] Shirely Ryan AbilityLab. Motricity Index. 2016l [cited 02.09.2020]. Available from: https://www.sralab.org/rehabilitation-measures/motricity-index.

[92] EQ-5D. EQ-5D-5L. About. 2020 [cited 03.09.2020]. Available from: https://euroqol.org/eq-5d-instruments/eq-5d-5l-about/.

[93] Hooker A. SF-36. In: Gellman M. D. and Turner J. R., editors. Encyclopedia of Behavioral Medicine 2013.

[94] European Commission. Guidelines on medical devices. 2015 [cited 15.07.2020]. Available from: http://ec.europa.eu/health/medical-devices/files/meddev/2_12_2_ol_en.pdf.

[95] Mayr A., Quirbach E., Picelli A., Kofler M., Smania N. and Saltuari L. Early robot-assisted gait retraining in non-ambulatory patients with stroke: a single blind randomized controlled trial. Eur J Phys Rehabil Med. 2018;54(6):819-826. Epub 2018/03/31. DOI: 10.23736/s1973-9087.18.04832-3.

[96] Hornby T. G., Campbell D. D., Kahn J. H., Demott T., Moore J. L. and Roth H. R. Enhanced gait-related improvements after therapist- versus robotic-assisted locomotor training in subjects with chronic stroke: a randomized controlled study. Stroke. 2008;39(6):1786-1792. Epub 2008/05/10. DOI: 10.1161/strokeaha.107.504779.

[97] Han E. Y., Im S. H., Kim B. R., Seo M. J. and Kim M. O. Robot-assisted gait training improves brachial-ankle pulse wave velocity and peak aerobic capacity in subacute stroke patients with totally dependent ambulation: Randomized controlled trial. Medicine. 2016;95(41):e5078-e5078. DOI: 10.1097/MD.0000000000005078.

[98] Chang W. H., Kim M. S., Huh J. P., Lee P. K. and Kim Y. H. Effects of robot-assisted gait training on cardiopulmonary fitness in subacute stroke patients: a randomized controlled study. Neurorehabil Neural Repair. 2012;26(4):318-324. Epub 2011/11/17. DOI: 10.1177/1545968311408916.

[99] Wall A., Borg J. and Palmcrantz S. Self-perceived functioning and disability after randomized conventional and electromechanically-assisted gait training in subacute stroke: A 6 months follow-up. NeuroRehabilitation. 2019;45(4):501-511.

[100] Geroin C., Picelli A., Munari D., Waldner A., Tomelleri C. and Smania N. Combined transcranial direct current stimulation and robot-assisted gait training in patients with chronic stroke: a preliminary comparison. Clin Rehabil. 2011;25(6):537-548. Epub 2011/03/16. DOI: 10.1177/0269215510389497.

[101] Dias D., Laíns J., Pereira A., Nunes R., Caldas J., Amaral C., et al. Can we improve gait skills in chronic hemiplegics? A randomised control trial with gait trainer. Eura Medicophys. 2007;43(4):499-504. Epub 2007/12/18.

[102] Pohl M., Werner C., Holzgraefe M., Kroczek G., Mehrholz J., Wingendorf I., et al. Repetitive locomotor training and physiotherapy improve walking and basic activities of daily living after stroke: a single-blind, randomized multicentre trial (DEutsche GAngtrainerStudie, DEGAS). Clin Rehabil. 2007;21(1):17-27. Epub 2007/01/11. DOI: 10.1177/0269215506071281.

[103] Hesse S., Tomelleri C., Bardeleben A., Werner C. and Waldner A. Robot-assisted practice of gait and stair climbing in nonambulatory stroke patients. J Rehabil Res Dev. 2012;49(4):613-622. Epub 2012/07/10. DOI: 10.1682/jrrd.2011.08.0142.

[104] Chua J., Culpan J. and Menon E. Efficacy of an Electromechanical Gait Trainer Poststroke in Singapore: A Randomized Controlled Trial. Arch Phys Med Rehabil. 2016;97(5):683-690. Epub 2016/01/24. DOI: 10.1016/j.apmr.2015.12.025.

[105] Sheffler L. R., Taylor P. N., Gunzler D. D., Buurke J. H., Ijzerman M. J. and Chae J. Randomized controlled trial of surface peroneal nerve stimulation for motor relearning in lower limb hemiparesis. Arch Phys Med Rehabil. 2013;94(6):1007-1014. Epub 2013/02/13. DOI: 10.1016/j.apmr.2013.01.024.

[106] Sheffler L. R., Taylor P. N., Bailey S. N., Gunzler D. D., Buurke J. H., MJ I. J., et al. Surface peroneal nerve stimulation in lower limb hemiparesis: effect on quantitative gait parameters. Am J Phys Med Rehabil. 2015;94(5):341-357. Epub 2015/03/25. DOI: 10.1097/phm.0000000000000269.

[107] Burridge J. H., Taylor P. N., Hagan S. A., Wood D. E. and Swain I. D. The effects of common peroneal stimulation on the effort and speed of walking: a randomized controlled trial with chronic hemiplegic patients. Clin Rehabil. 1997;11(3):201-210. Epub 1997/08/01. DOI: 10.1177/026921559701100303.

[108] Bogataj U., Gros N., Kljajić M., Aćimović R. and Malezic M. The rehabilitation of gait in patients with hemiplegia: a comparison between conventional therapy and multichannel functional electrical stimulation therapy. Phys Ther. 1995;75(6):490-502. Epub 1995/06/01. DOI: 10.1093/ptj/75.6.490.

[109] Embrey D. G., Holtz S. L., Alon G., Brandsma B. A. and McCoy S. W. Functional electrical stimulation to dorsiflexors and plantar flexors during gait to improve walking in adults with chronic hemiplegia. Arch Phys Med Rehabil. 2010;91(5):687-696. Epub 2010/05/04. DOI: 10.1016/j.apmr.2009.12.024.

[110] Spaich E. G., Svaneborg N., Jørgensen H. R. and Andersen O. K. Rehabilitation of the hemiparetic gait by nociceptive withdrawal reflex-based functional electrical therapy: a randomized, single-blinded study. Journal of neuroengineering and rehabilitation. 2014;11:81. Epub 2014/06/03. DOI: 10.1186/1743-0003-11-81.

[111] Kluding P. M., Dunning K., O'Dell M. W., Wu S. S., Ginosian J., Feld J., et al. Foot drop stimulation versus ankle foot orthosis after stroke: 30-week outcomes. Stroke. 2013;44(6):1660-1669. Epub 2013/05/04. DOI: 10.1161/strokeaha.111.000334.

[112] Bethoux F., Rogers H. L., Nolan K. J., Abrams G. M., Annaswamy T. M., Brandstater M., et al. The effects of peroneal nerve functional electrical stimulation versus ankle-foot orthosis in patients with chronic stroke: a randomized controlled trial. Neurorehabil Neural Repair. 2014;28(7):688-697. Epub 2014/02/15. DOI: 10.1177/1545968314521007.

[113] Bethoux F., Rogers H. L., Nolan K. J., Abrams G. M., Annaswamy T., Brandstater M., et al. Long-Term Follow-up to a Randomized Controlled Trial Comparing Peroneal Nerve Functional Electrical Stimulation to an Ankle Foot Orthosis for Patients With Chronic Stroke. Neurorehabil Neural Repair. 2015;29(10):911-922. Epub 2015/02/06. DOI: 10.1177/1545968315570325.

[114] Kottink A. I., Hermens H. J., Nene A. V., Tenniglo M. J., Groothuis-Oudshoorn C. G. and MJ I. J. Therapeutic effect of an implantable peroneal nerve stimulator in subjects with chronic stroke and footdrop: a randomized controlled trial. Phys Ther. 2008;88(4):437-448. Epub 2008/01/26. DOI: 10.2522/ptj.20070035.

[115] Daly J. J., Roenigk K., Holcomb J., Rogers J. M., Butler K., Gansen J., et al. A randomized controlled trial of functional neuromuscular stimulation in chronic stroke subjects. Stroke. 2006;37(1):172-178. Epub 2005/12/03. DOI: 10.1161/01.Str.0000195129.95220.77.

[116] Ng M. F., Tong R. K. and Li L. S. A pilot study of randomized clinical controlled trial of gait training in subacute stroke patients with partial body-weight support electromechanical gait trainer and functional electrical stimulation: six-month follow-up. Stroke. 2008;39(1):154-160. Epub 2007/11/17. DOI: 10.1161/strokeaha.107.495705.

[117] Tong R. K., Ng M. F. and Li L. S. Effectiveness of gait training using an electromechanical gait trainer, with and without functional electric stimulation, in subacute stroke: a randomized controlled trial. Arch Phys Med Rehabil. 2006;87(10):1298-1304. Epub 2006/10/07. DOI: 10.1016/j.apmr.2006.06.016.

[118] Macdonell R. A., Triggs W. J., Leikauskas J., Bourque M., Robb K., Day B. J., et al. Functional electrical stimulation to the affected lower limb and recovery after cerebral infarction. J Stroke Cerebrovasc Dis. 1994;4(3):155-160. Epub 1994/01/01. DOI: 10.1016/s1052-3057(10)80178-8.

[119] Bauer P., Krewer C., Golaszewski S., Koenig E. and Müller F. Functional electrical stimulation-assisted active cycling – therapeutic effects in patients with hemiparesis from 7 days to 6 months after stroke: a randomized controlled pilot study. Arch Phys Med Rehabil. 2015;96(2):188-196. Epub 2014/12/03. DOI: 10.1016/j.apmr.2014.09.033.

[120] de Sousa D. G., Harvey L. A., Dorsch S., Leung J. and Harris W. Functional electrical stimulation cycling does not improve mobility in people with acquired brain injury and its effects on strength are unclear: a randomised trial. J Physiother. 2016;62(4):203-208. Epub 2016/09/18. DOI: 10.1016/j.jphys.2016.08.004.

[121] Ferrante S., Pedrocchi A., Ferrigno G. and Molteni F. Cycling induced by functional electrical stimulation improves the muscular strength and the motor control of individuals with post-acute stroke. Europa Medicophysica-SIMFER 2007 Award Winner. Eur J Phys Rehabil Med. 2008;44(2):159-167. Epub 2008/04/18.

[122] Ambrosini E., Ferrante S., Pedrocchi A., Ferrigno G. and Molteni F. Cycling induced by electrical stimulation improves motor recovery in postacute hemiparetic patients: a randomized controlled trial. Stroke. 2011;42(4):1068-1073. Epub 2011/03/05. DOI: 10.1161/strokeaha.110.599068.

[123] Hwang D. Y., Lee H. J., Lee G. C. and Lee S. M. Treadmill training with tilt sensor functional electrical stimulation for improving balance, gait, and muscle architecture of tibialis anterior of survivors with chronic stroke: A randomized controlled trial. Technol Health Care. 2015;23(4):443-452. Epub 2015/03/05. DOI: 10.3233/thc-150903.

[124] Legg L.A., Lewis S.R., Schofield-Robinson O.J., Drummond A. and P. L. Occupational therapy for adults with problems in activities of daily living after stroke. Journal. 2017(7). Epub Epub Date. Original Publication. DOI: 10.1002/14651858.CD003585.pub3.

[125] Shirley Ryan AbilityLab. Functional Independence Measure. [cited 27.08.2015]. Available from: https://www.sralab.org/rehabilitation-measures/fimr-instrument-fim-fimr-trademark-uniform-data-system-fro-medical.

[126] Chehata V. J., Shatzer M. and Cristian A. Chapter 3 – Inpatient Rehabilitation Outcome Measures in Persons With Brain and Spinal Cord Cancer. Central Nervous System Cancer Rehabilitation, Elsevier. 2019:19-25. DOI: https://doi.org/10.1016/B978-0-323-54829-8.00003-2.

[127] Shirley Ryan AbilityLab. Motor Activity Log. [cited 28.08.2020]. Available from: https://www.sralab.org/rehabilitation-measures/motor-activity-log.

[128] Physiopedia. Chedoke-McMaster Stroke Assessment. 2020c [cited 01.09.2020]. Available from: https://physio-pedia.com/Chedoke-McMaster_Stroke_Assessment?utm_source=physiopedia&utm_medium=search&utm_campaign=ongoing_internal.

[129] Shirley Ryan AbilityLab. Chedoke Arm and Hand Activity Inventory. [cited 31.08.2020]. Available from: https://www.sralab.org/rehabilitation-measures/chedoke-arm-and-hand-activity-inventory-7.

[130] University of Kansas Medical Center. Stroke Impact Scale. 2020 [cited 28.08.2020]. Available from: http://www.kumc.edu/school-of-medicine/population-health/research-and-community-engagement/stroke-impact-scale.html.

[131] Shirley Ryan AbilityLab. Stroke Impact Scale. [cited 28.08.2020]. Available from: https://www.sralab.org/rehabilitation-measures/stroke-impact-scale.

[132] McDermott A. ABILHAND. 2012 [cited 31.08.2020]. Available from: https://www.strokengine.ca/en/assess/abilhand/.

[133] Vissers J. Jebsen Hand Function Test (JHFT). 2012 [cited 31.08.2020]. Available from: https://www.strokengine.ca/en/indepth/jhft_indepth/.

[134] Shirley Ryan AbilityLab. Jebsen Hand Function Test. [cited 31.08.2020]. Available from: https://www.sralab.org/rehabilitation-measures/jebsen-hand-function-test.

[135] van der Pas S. C., Verbunt J. A., Breukelaar D. E., van Woerden R. and Seelen H. A. Assessment of Arm Activity Using Triaxial Accelerometry in Patients With a Stroke. Arch Phys Med Rehabil. 2011;92(9):1437-1442. DOI: https://doi.org/10.1016/j.apmr.2011.02.021.

[136] Physiopedia. Fugl-Meyer Assessment of Motor Recovery after Stroke. 2020b [cited 31.08.2020]. Available from: https://physio-pedia.com/Fugl-Meyer_Assessment_of_Motor_Recovery_after_Stroke?utm_source=physiopedia&utm_medium=search&utm_campaign=ongoing_internal.

[137] Hogan J., Fasoli S., Aisen M. and Volpe B. Assessing the Motor Status Score: A Scale for the Evaluation of Upper Limb Motor Outcomes in Patients after Stroke. Neurorehabilitation and neural repair. 2002;16(283). DOI: 10.1177/154596802401105216.

[138] Shirley Ryan AbilityLab. Wolf Motor Function Test. [cited 31.08.2020]. Available from: https://www.sralab.org/rehabilitation-measures/wolf-motor-function-test.

[139] Shirley Ryan AbilityLab. Nottingham Assessment of Somato-Sensations. [cited 01.09.2020]. Available from: https://www.sralab.org/rehabilitation-measures/nottingham-assessment-somato-sensations.

[140] Wilson D., Baker L. and Craddock J. Functional Test for the Hemiparetic Upper Extremity. Motor task, rehabilitation, assessment. The American Journal of Occupational Therapy. 1984;38(3):159-164. DOI: https://doi.org/10.5014/ajot.38.3.159.

[141] Joseph C. and Rhoda A. Activity limitations and factors influencing functional outcome of patients with stroke following rehabilitation at a specialised facility in the Western Cape. African Health Sciences. 2013;13(3):646-654. DOI: 10.4314/ahs.v13i3.18.

[142] Physiopedia. Action Research Arm Test (ARAT). 2020d [cited 01.09.2020]. Available from: https://physio-pedia.com/Action_Research_Arm_Test_(ARAT)?utm_source=physiopedia&utm_medium=search&utm_campaign=ongoing_internal.

[143] Teasell R., Hussein N., Mirkowski M., Vanderlaan D., Saikaley M., Langval M., et al. Hemiplegic Upper Extremity Rehabilitation. 2020 [cited 21.09.2020]. Available from: http://ebrsr.com/sites/default/files/EBRSR%20Handbook%20Chapter%204_Upper%20Extremity%20Post%20Stroke_ML.pdf.

[144] Marvin K. Frenchay Arm Test (FAT). 2012 [cited 02.09.2020]. Available from: https://www.strokengine.ca/en/assess/fat/.

[145] Wist S., Clivaz J. and Sattelmayer M. Muscle strengthening for hemiparesis after stroke: A meta-analysis. Annals of Physical and Rehabilitation Medicine. 2016;59(2):114-124. DOI: https://doi.org/10.1016/j.rehab.2016.02.001.

[146] Physiopedia. Muscle Strength. 2020e [cited 03.09.2020]. Available from: https://physio-pedia.com/Muscle_Strength?utm_source=physiopedia&utm_medium=related_articles&utm_campaign=ongoing_internal.

[147] Shirely Ryan AbilityLab. Trunk Control Test. 2016j [cited 02.09.2020]. Available from: https://www.sralab.org/rehabilitation-measures/trunk-control-test.

[148] Figueiredo S. Modified Ashworth Scale. 2011b [cited 02.09.2020]. Available from: https://www.strokengine.ca/en/indepth/mashs_indepth/.

[149] Shirely Ryan AbilityLab. Hand-held Dynamometer/Grip Strength. 2014 [cited 03.09.2020]. Available from: https://www.sralab.org/rehabilitation-measures/hand-held-dynamometergrip-strength.

[150] Naqvi U. and Sherman A. I. Muscle Strength Grading. Journal. 2019. Epub Epub Date. Original Publication.

[151] Volpe B. T., Krebs H. I., Hogan N., Edelsteinn L., Diels C. M. and Aisen M. L. Robot training enhanced motor outcome in patients with stroke maintained

over 3 years. American Academy of Neurology. 1999;53(8):1874-1876. DOI: 10.1212/WNL.53.8.1874.

[152] Ramos-Lima M., Carvalho Brasileiro I., de Lima T. and Braga-Neto P. Quality of life after stroke: impact of clinical and sociodemographic factors. Clinics (Sao Paulo). 2018;73(e418). DOI: 10.6061/clinics/2017/e418.

[153] Mehrholz J., Pollock A., Pohl M., Kugler J. and Elsner B. Systematic review with network meta-analysis of randomized controlled trials of robotic-assisted arm training for improving activities of daily living and upper limb function after stroke. Journal of neuroengineering and rehabilitation. 2020;17(1):83. Epub 2020/07/02. DOI: 10.1186/s12984-020-00715-0.

[154] Rodgers H., Bosomworth H., Krebs H. I., van Wijck F., Howel D., Wilson N., et al. Robot assisted training for the upper limb after stroke (RATULS): a multicentre randomised controlled trial. Lancet. 2019;394(10192):51-62. Epub 2019/05/28. DOI: 10.1016/s0140-6736(19)31055-4.

[155] Bernhardt J. and Mehrholz J. Robotic-assisted training after stroke: RATULS advances science. Lancet. 2019;394(10192):6-8. Epub 2019/05/28. DOI: 10.1016/s0140-6736(19)31156-0.

[156] Kayabınar E., Özalp M., Koçyiğit M. F., As İ. and Elbasan B. The effects of robotic and conventional gait training in addition to neurodevelopmental treatment on balance, mobility, and health-related quality of life in patients with stroke. Neurological Sciences and Neurophysiology. 2019;36(2):112-119.

[157] Lee H. J., Lee S. H., Seo K., Lee M., Chang W. H., Choi B. O., et al. Training for Walking Efficiency With a Wearable Hip-Assist Robot in Patients With Stroke: A Pilot Randomized Controlled Trial. Stroke. 2019;50(12):3545-3552.

[158] Nam Y. G., Lee J. W., Park J. W., Lee H. J., Nam K. Y., Park J. H., et al. Effects of Electromechanical Exoskeleton-Assisted Gait Training on Walking Ability of Stroke Patients: A Randomized Controlled Trial. Archives of Physical Medicine & Rehabilitation. 2019;100(1):26-31.

[159] Rojek A., Mika A., Oleksy L., Stolarczyk A. and Kielnar R. Effects of Exoskeleton Gait Training on Balance, Load Distribution, and Functional Status in Stroke: A Randomized Controlled Trial. Frontiers in neurology [electronic resource]. 2019;10:1344.

[160] Awad L. N., Reisman D. S., Pohlig R. T. and Binder-Macleod S. A. Reducing the cost of transport and increasing walking distance after stroke: a randomized controlled trial on fast locomotor training combined with functional electrical stimulation. Neurorehabilitation and Neural Repair 2016 Aug;30(7):661-670. 2016.

[161] Bae Y. H., Ko Y. J., Chang W. H., Lee J. H., Lee K. B., Park Y. J., et al. Effects of Robot-assisted Gait Training Combined with Functional Electrical Stimulation on Recovery of Locomotor Mobility in Chronic Stroke Patients: A Randomized Controlled Trial. J Phys Ther Sci. 2014;26(12):1949-1953. Epub 2014/12/30. DOI: 10.1589/jpts.26.1949.

[162] Cho M. K., Kim J. H., Chung Y. and Hwang S. Treadmill gait training combined with functional electrical stimulation on hip abductor and ankle dorsiflexor muscles for chronic hemiparesis. Gait Posture. 2015;42(1):73-78.

[163] Everaert D. G., Stein R. B., Abrams G. M., Dromerick A. W., Francisco G. E., Hafner B. J., et al. Effect of a foot-drop stimulator and ankle-foot orthosis on walking performance after stroke: a multicenter randomized controlled trial. Neurorehabilitation & Neural Repair. 2013;27(7):579-591.

[164] Ji S. G., Cha H. G., Kim M. K. and Lee C. R. The effect of mirror therapy integrating functional electrical stimulation on the gait of stroke patients. Journal of Physical Therapy Science 2014 Apr;26(4):497-499. 2014.

[165] Kottink A. I., Tenniglo M. J., de Vries W. H., Hermens H. J. and Buurke J. H. Effects of an implantable two-channel peroneal nerve stimulator versus conventional walking device on spatiotemporal parameters and kinematics of hemiparetic gait. Journal of Rehabilitation Medicine. 2012;44(1):51-57.

[166] Lee D. and Lee G. Effect of afferent electrical stimulation with mirror therapy on motor function, balance, and gait in chronic stroke survivors: a randomized controlled trial. Eur J Phys Rehabil Med. 2019;55(4):442-449.

[167] Lee K. Balance training with electromyogram-triggered functional electrical stimulation in the rehabilitation of stroke patients. Brain Sciences. 2020;10(2).

[168] Lo H. C., Hsu Y. C., Hsueh Y. H. and Yeh C. Y. Cycling exercise with functional electrical stimulation improves postural control in stroke patients. Gait & Posture 2012 Mar;35(3):506-510. 2012.

[169] Morone G., Fusco A., Di Capua P., Coiro P. and Pratesi L. Walking training with foot drop stimulator controlled by a tilt sensor to improve walking outcomes: a randomized controlled pilot study in patients with stroke in subacute phase. Stroke Research and Treatment. 2012;2012:523564.

[170] Tan Z., Liu H., Yan T., Jin D., He X., Zheng X., et al. The effectiveness of functional electrical stimulation based on a normal gait pattern on subjects with early stroke: a randomized controlled trial. BioMed Research International 2014;(545408):Epub. 2014.

[171] You G., Liang H. and Yan T. Functional electrical stimulation early after stroke improves lower limb motor function and ability in activities of daily living. NeuroRehabilitation. 2014;35(3):381-389.

[172] Zheng X., Chen D., Yan T., Jin D., Zhuang Z., Tan Z., et al. A Randomized Clinical Trial of a Functional Electrical Stimulation Mimic to Gait Promotes Motor Recovery and Brain Remodeling in Acute Stroke. Behavioural Neurology. 2018;2018:8923520.

[173] European Network for Health Technology Assessment (EUnetHTA Work Package WP5). HTA Core Model for the production of Rapid Relative Effectiveness Assessments (version 4.2). 2015 [cited 21.09.2020]. Available from: https://eunethta.eu/wp-content/uploads/2018/06/HTACoreModel_ForRapidREAs4.2-3.pdf.

Appendix

Evidence tables of individual studies included for clinical effectiveness and safety

Table A-1: Functional electrical stimulation (FES): Results from randomised controlled trials (1b only) published between 2012 and 2020

Author, year	Bauer, 2015 [119]	Bethoux, 2014/2015 [112, 113]	de Sousa, 2016 [120]	Hwang, 2015 [123]	Kluding, 2013 [111]	Sheffler, 2013/2015 [105, 106]
Study design, LoE, quality	RCT, 1b, +	RCT, 1b, ++	RCT, 1b, +	RCT, 1b, +	RCT, 1b, ++	RCT, 1b, +
Country	GER	USA	AUS	KOR	USA	USA
COI/Sponsor	NR	Innovative Neurotronics	None declared	None declared	Funded by Bioness Inc.	Odstock Medical Ltd Guilford & Son Ltd Orthotics and Prosthetic Center SAS Institute Inc
Intervention/ Product	Active leg cycling with FES (4 w.)	FES (WalkAide® System) and standard rehabilitation(6 m.)	FES Cycling and standard rehabilitation(4 w.)	Tilt sensor FES (WalkAide® System) with treadmill training (4 w.)	Foot Drop System (NESS L300) and standard rehabilitation(30 w.)	Peroneal nerve stimulator (Oddstock Dropped-Foot Stimulator)
Comparator	Active leg cycling without FES	Conventional AFO and standard rehabilitation	Standard rehabilitation alone	Treadmill training with placebo FES (sham intervention)	Conventional AFO and standard rehabilitation	Standard rehabilitation (incl. AFO in 48/56 pts)
Number of pts (IG/CG)	40 (21/19)	495 (242/253)	40 (20/20)	32 (16/16)	197 (99/98)	110 (54/56)
Inclusion criteria	■ 18 years or older ■ Diagnosis of a first stroke (7d to 6m.) resulting in severe hemiparesis with a grade less than 3 for the musculus quadriceps on the Medical Research Council scale ■ FAC: 2 or lower ■ Pts had to understand informed consent ■ Pts had to be able to cycle for 20 min	■ Stroke onset ≥6 months before enrolment ■ Positive response to peroneal nerve stimulation testing (able to safely clear toes in swing phase on the involved lower extremity, defined as >−5° plantar flexion, with the FES device (determined at fitting) ■ Adequate mental function (MMSE score >17 and BDI <29) ■ Adequate communication; is non-aphasic and can verbalize commands and communicate answers to study measures (questionnaires) ■ Ability to ambulate at least 10 meters (with or without AD) at a speed >0.0 m/s and <0.8 m/s ■ No use of existing electrical stimulation devices (ICD, pacemaker, spinal stimulation, TENS) ■ Medicare or Medicare Advantage eligibility	■ First time stroke or any other non-progressive acquired brain injury; ■ hemiparesis with composite strength in the affected lower limb < 19/20 points; ■ less than 6 months after acquired brain injury; ■ ability to sit supported for 40 minutes; and sufficient communication skills to indicate yes/no verbally or via gestures	■ experienced at least one stroke, those who had had a stroke more than 6 months ago, ■ Ability to walk more than 15 meters independently without a walking aid, scored at least 24 in the Mini-Mental State Examination (MMSE), ■ No problems with auditory or visual function, were classified as 2nd grade or lower on ankle plantar flexor response on the Modified Ashworth Scale, ■ Between the 2nd and 4th stages on the Brunnstrom Stages	■ At least 1 stroke ≥3 mo before study enrollment, resulting in drop foot ■ Ankle dorsiflexion response with test stimulation in sitting and standing, and adequate ankle and knee stability during gait with test stimulation ■ Medically stable ■ Score ≥24 on the Mini Mental State Examination (MMSE), or have a competent caregiver if <24 ■ Age ≥18 y or older ■ Able to walk ≥10 meters with a maximum of 1 person assist ■ Self-selected gait speed ≤0.80 m/s without orthotic effect	■ age ≥18 years, ■ ≥12 weeks poststroke with unilateral hemiparesis, and ankle dorsiflexion strength of ≤4/5 on the Medical Research Council scale. ■ Subjects were required to ambulate ≥30ft without an AFO, score ≥24 on the BBS, and demonstrate correction of footdrop using a PNS without evidence of knee hyperextension during stance

Author, year	Bauer, 2015 [119]	Bethoux, 2014/2015 [112, 113]	de Sousa, 2016 [120]	Hwang, 2015 [123]	Kluding, 2013 [111]	Sheffler, 2013/2015 [105, 106]
Age of patients (yrs), mean ±SD	59 ±14 vs. 64 ±11); diff. n. s. (p>0.05)	63.87 ±11.33 vs. 64.30 ±12.01; diff. n. s. (p>0.05)	62 ±15 vs. 60 ±16; p value NR	50.00 ±7.55 vs. 49.47 ±5.01; diff. n. s. (p>0.05)	60.71±12.24 vs. 61.58±10.98; diff. n. s. (p>0.05)	52.8 ±12.2 vs. 53.2 ±10.1; diff. n. s. (p>0.05)
Gender female, n (%)	7 (38.9) vs. 9 (50); diff. n. s. (p>0.05)	95 (39.26) vs. 96 (37.94); diff. n. s. (p>0.05)	6 (30) vs. 7 (35); p value NR	6 (40) vs. 7 (47)	48 (60.8) vs. 31 (39.2); diff. s. s. (p<0.05)	24 (44.4) vs. 19 (33.9); diff. n. s. (p>0.05)
Stadium of stroke	Subacute	Chronic	Subacute	Chronic	Chronic	Chronic
Setting	Inpatient	Outpatient	Inpatient	Inpatient	Inpatient	Outpatient
Time since stroke	Time since stroke onset (d): 62 ±43 vs. 42 ±45; diff. n. s. (p>0.05)	Time post onset of Stroke (years, mean ± SD): 6.90 ± 6.43 vs. 6.86 ± 6.64; diff. n. s. (p>0.05)	Time since ABI (d), median (IQR): 34 (22 to 49) vs. 38 (24 to 72)	Time since onset of stroke (days): 192.53 ±18.79 vs. 194.07 ±18.95 (p>0.05)	Years from stroke to randomization: 4.77±5.29 vs. 4.34±4.1; diff. n. s. (p>0.05)	>12w. poststroke (not further specified)
Primary outcome measures	Functional ambulation classification (FAC) and performance-oriented mobility assessment (POMA)	**Test for non-inferiority:**10-Meter Walk Test (10MWT), a composite of the Mobility, Activities of Daily Living/ Instrumental Activities of Daily Living, and Social Participation subscores on the Stroke Impact Scale (SIS), and de-vice-related serious adverse event rate	Mobility and strength of the knee extensors of the affected lower limb	Balance: Timed Up and Go (TUG) test and Berg Balance Scale (BBS) Gait: 10-meter walk test (10MWT); Structure of the tibialis anterior: ultrasound	Walking speed assessed with a 10-meter walk test (10MWT)	Lower extremity Fugl-Meyer (FM) Assessment
Secondary outcome measures	leg subscale of the motricity index (MI) and the modified Ashworth scale	6-Minute Walk Test, GaitRite Functional Ambulation Profile (FAP), Modified Emory Functional Ambulation Profile (mEFAP), Berg Balance Scale (BBS), Timed Up and Go (TUG), individual SIS domains, and Stroke-Specific Quality of Life measures	Strength of the knee extensors of the unaffected lower limb, strength of keymuscles of the affected lower limb and spasticity of the affected plantar flexors.	NR	Body structure and function (lower extremity Fugl-Meyer), several activity measures to assess functional mobility (Timed up and go), walking endurance (6-minute walk test [6MWT]), and balance (Berg balance scale; Functional reach test), and a participation-level measure (Stroke Impact Scale) User Satisfaction	Modified Emory FunctionalAmbulation Profile (mEFAP) and the Stroke Specific Quality of Life (SSQOL) Score Activity limitation was assessed with the mEFAP
Length of Follow-up	2 w. after treatment	6 m. & 12 m. post-hoc follow-up analysis	Post-treatment	Post-treatment	Post-treatment	Up to 6 m. post-treatment
Loss to follow-up, n (%)	Postintervention: 2 (9.5) vs. 1 (5.3) Follow-up: 12 (57.1) vs. 7 (36.8)	55 (22.73) vs.41 (16.2)	1 (5) vs. 0 (0)	1 (6.3) vs. 1 (6.3)	0 (0) vs. 0 (0)[55]	Post-treatment: 8 (14.8) vs. 6 (10.7) 3 m.: 10 (18.5) vs. 7 (12.5) 6 m.: 15 (27.8) vs. 11 (19.6)
Ability to walk	**FAC:** *MD (pre- to postintervention):* 2 ±0 vs. 1 ±0; diff. s. s. (p<0.05) *MD (preintervention to follow-up):* 2 ±0 vs. 1 ±0; diff. n. s. (p>0.05)	**FAP** (MD of improvements at 6 m.): 2.3; n. s. (p>0.05) **mEFAP** (MD of improvements at 6 m.): -76.0; n. s. (p>0.05)[56]	Functional Independence Measure (bed-chair transfer, walking and stairs; MD of improvement between groups): −0.3, n. s. (95%CI: −3.2 to 2.7)	NR	Change in SIS mobility scores: 7.14±15.04 vs. 3.19±14.30; diff. n. s. (p>0.05)	*FM:* no significant treatment group main effect (P=.797) or treatment group by time interaction effect (P=.321) on FM raw scores

[55] Data from patients lost to follow-up (25 vs. 10) was imputed.

Author, year	Bauer, 2015 [119]	Bethoux, 2014/2015 [112, 113]	de Sousa, 2016 [120]	Hwang, 2015 [123]	Kluding, 2013 [111]	Sheffler, 2013/2015 [105, 106]
Ability to walk *(continuation)*	**POMA:** MD (pre- to postintervention): 4 ±1 vs. 2 ±0; diff. s. s. (p<0.004) MD (preintervention to follow-up): 5 ±1 vs. 3 ±1; diff. n. s. (p>0.05)				Change in Fugl-Meyer Lower Extremity Score: 0.38±3.56 vs. 1.04±3.26; diff. n. s. (p>0.05)	*mEFAP:* no significant treatment group main effect (P=.968) or treatment group by time interaction effect (P>.999) on mEFAP raw score
Walking speed	**10 MWT** (postintervention, mean ±SD): 55.4 ±27.8s vs. 22.3 ±12s; diff. s. s. (p=0.049)	**10 MWT** Test at 6 m. (m/s): δ = −0.2 m/s (p< 0.0001; test for non-inferiority)[56]	NR	**10 MWT** (post-treatment, in sec): −7.51 ± 2.66 vs. −5.24 ± 1.81; diff. s. s. (p<0.05)	**10 MWT:** Change in comfortable gait speed, m/s: 0.14±0.16 vs. 0.15±0.14; diff. n. s. (p>0.05) Change in fast gait speed, m/s: 0.13±0.16 vs. 0.17±0.18; diff. n. s. (p>0.05)	At last follow-up: 0.44 ±0.28 vs. 0.47 ±0.24 no significant treatment group main effect or treatment group by time interaction effect
Walking distance	NR	**6MWT** (MD of improvements at 6 m. in m): 15.1; n. s. (p>0.05)[56]	NR	NR	Change in 6-min walk distance, m: 40.9±62.1 vs. 48.6±51.1; diff. n. s. (p>0.05)	NR
Balance	NR	**BBS** (MD of improvements at 6 m.): 1.3; n. s. (p>0.05) **TUG** (MD of improvements at 6 m. in s): 0.7; n. s. (p>0.05)[56]	NR	TUG (post-treatment, in sec): −8.28 ±2.76 vs. −4.89 ±1.81; diff. s. s. (p<0.001) BBS score (post-treatment): 12.13 ± 3.44 vs. 8.00 ± 2.98; diff. s. s. (p<0.01)	Change in TUG, s: −5.93±13.06 vs. −4.38±21.37; diff. n. s. (p>0.05) Change in BBS score: 1.97±6.08 vs. 3.75±4.62; diff. s. s. (p<0.05)	NR
Motricity index/muscle strength	MD (pre- to postintervention): 11 ±3 vs. 12 ±3; diff. n. s. (p>0.05) MD (preintervention to follow-up): 17 ±4 vs. 15 ±3; diff. n. s. (p>0.05)	NR	Strength of the knee extensors of the affected lower limb [57] (MD of improvement in Nm between groups): 7.5; n. s. (95%CI: −5.1 to 20.2) Strength of key muscles of the affected lower limb[58] (MD of improvement between groups): 3.0; s. s. (95%CI: 1.3 to 4.8) Strength of the knee extensors of the unaffected lower limb[57] (MD of improvement between groups): 0.9, n. s. (95%CI: −9.4 to 11.2) Spasticity (muscle reaction item of the Tardieu Scale MD of improvement between groups): 0.3; n. s. (95%CI: −0.5 to 1.0)	NR	NR	NR

[56] A post-hoc analysis indicated FES to be non-inferior compared to AFO after 12 m. f/u as well. No statistically significant between-group differences were found for primary or secondary endpoints.

[57] Maximal force was measured in Nm with a hand-held dynamometer

[58] The strength of the knee flexors and extensors, ankle dorsiflexors and plantar flexors were assessed using manual muscle testing. Scores for the four muscle groups were combined and treated as a composite measure of lower limb strength, with 20 points representing the maximum score.

Author, year	Bauer, 2015 [119]	Bethoux, 2014/2015 [112, 113]	de Sousa, 2016 [120]	Hwang, 2015 [123]	Kluding, 2013 [111]	Sheffler, 2013/2015 [105, 106]
Acceptance of rehabilitation device	NR	Discontinued because of dissatisfaction with device: 7 (2.9) vs. 10 (4)	NR	NR	User satisfaction at week 12: 21.9±2.4 vs.19.0±4.4 (95% CI:, 1.71–3.87; p<0.001) User satisfaction at week 30: 21.8±2.9 vs.19.1±4.0 (95% CI 1.64–3.74; p<0.001) Note: instrument NR	NR
Health related Quality of Life	NR	**SSQoL** (MD of improvements at 6 m.): 1.0; n. s. (p>0.05) **Stroke Impact Scale (SIS)**: δ = −15 points; (P<0.0001; test for non-inferiority)[56] **SIS:** n. s. MDs of improvement at 6 m. in 8 subscores (p>0.05)	NR	NR	NR	*SSQoL*: no significant treatment group main effect (PZ.360) or treatment group by time interaction effect (PZ.627) on SSQOL raw scores
Overall complications, n (%)	0 (0) vs. 0 (0)	422 vs. 436	NR	NR	Not estimable	NR
Serious AE, n (%)	0 (0) vs. 0 (0)	**Unrelated to device**: 25 (2.9) vs. 16 (1.9) **Related to device**: 0 (0) vs. 2 (0.2) Test for noninferiority: δ = −3% devicerelated SAE rate; p< 0.001; test for non-inferiority)[56]	NR	NR	14 vs. 6 [59] Related to device: 0 (0) vs. 0 (0)	NR
AE, n (%)	0 (0) vs. 0 (0)	*Falls:* 173 (20.2) vs. 175 (20.4) *"Other" (e.g., fatigue or muscle weakness, other medical conditions):* 189 (22.0) vs. 235 (27.4) Skin irritation: 34 (3.9) vs. 10 (1.2) Muscle soreness: 15 (1.75) vs. 15 (1.75)	NR	NR	219 vs. 147; diff. s. s. (p<0.01 Related to device: 130 vs. 50; diff. s. s. (p<0.01)	NR

Abbreviations: 10MWT – 10-meter walk test; ABI – acquired brain injury; AD – assistive device; AE – adverse events; AFO – ankle foot orthosis; AUS – Australia; BBS – berg balance scale; BDI – Beck Depression Inventory; CG – control group; CI – confidence interval; COI – conflict of interest; d – day(s); diff. – difference; FAC – functional ambulation category; FAP – functional ambulation profile; FES – functional electrical stimulation; FM – Fugl-Meyer; GER – Germany; ICD – implantable cardioverter-defibrillator; IG – intervention group; KOR – South Korea; LoE – level of evidence; m. – month(s); m/s – minutes per second; MD – mean difference; mEFAP – modified emory functional ambulation profile; MI – motricity index; MMSE – mini mental state examination; n. s. – not statistically significant; NR – not reported; PNS – peroneal nerve stimulator; POMA – performance oriented mobility assessment; pts – patients; RCT – randomised controlled trial; s. s. – statistically significant; SAE – serious adverse events; SD – standard deviation; SIS – stroke impact scale; TENS – transcutaneous electrical stimulation; TUG – timed up and go test; USA – United States of America; w. – week(s); yrs – years.

[59] p values not reported.

Risk of bias tables and GRADE evidence profile

Internal validity of the included studies was judged by two independent researchers. In case of disagreement, a third researcher was involved to solve the differences. A more detailed description of the criteria used to assess the internal validity of the individual study designs can be found in the Internal Manual of the AIHTA [2] and in the Guidelines of EUnetHTA [3].

Table A-2: Risk of bias – AGREE II quality appraisal of the AWMF guideline on the use of rehabilitative therapy for patients suffering from arm paresis after a stroke

Domain	Item	AGREE II Score		
		Single Score	Justification	Overall Score
1. Scope and purpose	1. The overall objective(s) of the guideline is (are) specifically described.	7		**7**
	2. The health question(s) covered by the guideline is (are) specifically described.	7		
	3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	7		
2. Stakeholder involvement	4. The guideline development group includes individuals from all the relevant professional groups.	7		**6.6**
	5. The views and preferences of the target population (patients, public, etc.) have been sought.	6	Questionable if preferences of patient groups are sufficiently represented.	
	6. The target users of the guideline are clearly defined.	7		
3. Rigor of development	7. Systematic methods were used to search for evidence.	7		**6.6**
	8. The criteria for selecting the evidence are clearly described.	7		
	9. The strengths and limitations of the body of evidence are clearly described.	6	GRADE evidence tables are not provided.	
	10. The methods for formulating the recommendations are clearly described.	7		
	11. The health benefits, side effects and risks have been considered in formulating the recommendations.	7		
	12. There is an explicit link between the recommendations and the supporting evidence.	7		
	13. The guideline has been externally reviewed by experts prior to its publication.	5	No precise description is given on who conducted the external review.	
	14. A procedure for updating the guideline is provided.	7		
4. Clarity of presentation	15. The recommendations are specific and unambiguous.	7		**7**
	16. The different options for management of the condition or health issue are clearly presented.	7		
	17. Key recommendations are easily identifiable.	7		

Domain	Item	AGREE II Score		
		Single Score	Justification	Overall Score
5. Applicability	18. The guideline describes facilitators and barriers to its application.	4	No specific description about facilitators and barriers.	4.75
	19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	3	No tools, advice, check lists, user manuals are provided yet. (Higher rating is possible if more information will be uploaded in the near future.)	
	20. The potential resource implications of applying the recommendations have been considered.	6	Methods by which cost information was sought are not mentioned.	
	21. The guideline presents monitoring and/or auditing criteria.	6	No clearly defined indicators for measuring the guideline recommendation are given.	
6. Editorial independence	22. The views of the funding body have not influenced the content of the guideline.	7		7
	23. Competing interests of guideline development group members have been recorded and addressed.	7		
Overall Guideline Assessment	1. Rate the overall quality of this guideline	7 (aggregated: 6.5)		
Overall Guideline Assessment	2. I would recommend this guideline for use.	Yes		

Table A-3: Risk of bias of RCTs for robot assisted lower extremities stroke rehabilitation identified by the update search

First author, year	Kayabinar, 2019 [156]	Lee, 2019 [157]	Nam, 2019 [158]	Rojek, 2019 [159]	Wall, 2019 [99]
1. Were participants randomly allocated (selection bias)?	Y	Y[60]	Y[61]	U[62]	U[62]
2. Was assessment performed blinded (detection bias)?	U	U	Y	Y	Y
3. Allocation concealment (selection bias)?	U	Y	U	Y	U
4. Prospective design?	Y	Y	Y	Y	Y
5. Clear definition of eligibility criteria?	Y	Y	Y	Y	Y
6. Comparability of experimental and control groups at baseline?	N	Y	N[63]	N[64]	Y
7. Clear definition and adequate assessment of study outcomes?	Y	Y	Y	Y	Y
8. Comparable treatment of randomized groupsaside from investigated effects?	Y	Y	Y	Y	Y
9. Reporting of side effects?	N	Y	Y	N	N
10. Intention-to-treat analysis reported?	N	N	N	N	N
11. (Almost) Complete outcome data (no attrition bias)?	Y	Y[65]	Y[66]	N[67]	N[68]
12. No selective reporting (no reporting bias)?	U[69]	Y	Y	N[70]	U
13. Adequate follow up assessment(s)?	N	N	N	N	Y
14. Do the results sufficiently support the conclusions reported?	N	N[71]	N	N	Y
Overall RoB (quality rating)	**High (--)**	**High (-)**	**High (--)**	**High (--)**	**High (-)**
LoE	**2b**	**2b**	**2b**	**2b**	**2b**

Abbreviations: LoE – level of evidence; N – no; RoB – risk of bias; U – unclear; Y – yes.

[60] randomisation method: random number table with a computer

[61] Study authors used an adequate method of randomisation, namely a random number table

[62] Method of randomisation not reported

[63] pts in the intervention group are significantly younger that pts in the control group

[64] Insufficient reporting; no statistical testing of baseline differences between IG and CG. BI s. s. differed between groups at baseline.

[65] IG: 14/14 (100%) // CG: 12/14 (85.7%)

[66] IG: 18/20 (90%) // CG: 16/20 (80%)

[67] IG: 23/30 (76.7%) // CG: 21/30 (70%)

[68] IG: 15/17 (88.2%) // CG: 13/17 (76.5%)

[69] No study protocol available.

[70] Only a retrospectively registered study protocol is available

[71] Aauthors promote GEMS based on imprecise effect estimates favoring the IG

Table A-4: Risk of bias of RCTs for FES lower extremities identified by the update search (adapted version of the PEDRO risk of bias tool [81]) – part 1/3

First author, year	Awad, 2016 [160]	Bae, 2014 [161]	Bauer, 2015 [119]	Bethoux, 2014/ 2015 [112, 113]	Cho, 2015 [162]	de Sousa, 2016 [120]	Everaert, 2013 [163]
1. Were participants randomly allocated (selection bias)?	U	Y	Y	Y	U	Y	Y
2. Was assessment performed blinded (detection bias)?	Y	Y	Y	N	U	Y	N
3. Allocation concealment (selection bias)?	U	Y	Y	Y	Y	Y	Y
4. Prospective design?	Y	Y	Y	Y	Y	Y	Y
5. Clear definition of eligibility criteria?	Y	Y	Y	Y	Y	Y	Y
6. Comparability of experimental and control groups at baseline?	Y	Y	Y	Y	Y	Y	Y
7. Clear definition and adequate assessment of study outcomes?	N[72]	Y	Y	Y	N[73]	Y	Y
8. Comparable treatment of randomized groups aside from investigated effects?	Y	Y	Y	Y	Y	Y	U
9. Reporting of side effects?	N	N	Y	Y	N	N	Y
10. Intention-to-treat analysis reported?	N	N	Y	Y	N	Y	N
11. (Almost) Complete outcome data (no attrition bias)?	Y[74]	U[75]	Y[76]	N[77]	U[78]	Y[79]	Y[80]
12. No selective reporting (no reporting bias)?	U[81]	U[81]	Y	Y	U[81]	Y	U[82]
13. Adequate follow up assessment(s)?	Y	N	Y	Y	N	N	Y
14. Do the results sufficiently support the conclusions reported?	N	N[83]	Y	Y	N	Y	Y
Overall RoB (quality rating)	**High (--)**	**High (-)**	**Low (++)**	**Low (++)**	**High (--)**	**Low (+)**	**High (-)**
LoE	**2b**	**2b**	**1b**	**1b**	**2b**	**1b**	**2b**

Abbreviations: LoE – level of evidence; N – no; RoB – risk of bias; U – unclear; Y – yes.

72 Primary objective of the study was to assess the effect of FastFES. However, the primary outcome was clearly a surrogate outcome.

73 No precise definition of primary/secondary outcomes. Instruments to measure outcomes are fine.

74 IG1: 14/17 (82.4%) // IG2: 16/16 (100%) // IG3: 15/17 (88.2%)

75 intransparent reporting of trial (n of enrolled pts, n of analysed pts, etc.)

76 IG: 19/21 (90.5%) // CG: 18/19 (94.7%). No attrition bias post-treatment, but increased attrition bias at the latest follow-up assessment.

77 IG: 187/242 (77.3%) // CG: 212/253 (83.8%)

78 Unclear reporting; overall 31/36 patients (86%) were analysed.

79 IG: 19/20 (95%) // CG: 20/20 (100%)

80 Arm1: 38/43 (88.4%) // Arm2: 31/43 (72.1%) // Arm3: 24/30 (80%)

81 No study protocol available.

82 10-meter walk test changed from primary endpoint in the protocol to a secondary endpoint in the publication. No information on the rationale provided.

83 Authors favor the CG because there is no risk of adverse events. However, adverse events are not reported.

Table A-5: Risk of bias of RCTs for FES lower extremities identified by the update search (adapted version of the PEDRO risk of bias tool [81]) – part 2/3

First author, year	Hwang, 2015 [123]	Ji, 2014 [164]	Kluding, 2013 [111]	Kottink, 2012 [165]	Lee, 2019 [166]	Lee, 2020 [167]	Lo, 2012 [168]
1. Were participants randomly allocated (selection bias)?	Y	U	Y	Y	Y	Y	U
2. Was assessment performed blinded (detection bias)?	Y	U	Y	N	Y	Y	U
3. Allocation concealment (selection bias)?	Y	U	Y	Y	Y	Y	U
4. Prospective design?	Y	Y	Y	Y	Y	Y	Y
5. Clear definition of eligibility criteria?	Y	N	Y	Y	Y	Y	Y
6. Comparability of experimental and control groups at baseline?	Y	Y	Y	N[84]	Y	Y	Y
7. Clear definition and adequate assessment of study outcomes?	Y	N	Y	Y	Y	Y	N[85]
8. Comparable treatment of randomized groups aside from investigated effects?	Y	Y	Y	Y	Y	Y	Y
9. Reporting of side effects?	N	N	Y	N	N	N	N
10. Intention-to-treat analysis reported?	N	N	Y	N	N	N	N
11. (Almost) Complete outcome data (no attrition bias)?	Y[86]	U[87]	Y[88]	N[89]	Y[90]	Y[91]	U[92]
12. No selective reporting (no reporting bias)?	U[93]	U[93]	Y	U[93]	U[93]	U[93]	U[93]
13. Adequate follow up assessment(s)?	N	N	N	Y	N	N	N
14. Do the results sufficiently support the conclusions reported?	Y	N	Y	Y	N	N	Y
Overall RoB (quality rating)	**Moderate (+)**	**High (--)**	**Low (++)**	**High (--)**	**High (-)**	**High (-)**	**High (--)**
Evidence level	**1b**	**2b**	**1b**	**2b**	**2b**	**2b**	**2b**

Abbreviations: LoE – level of evidence; N – no; RoB – risk of bias; U – unclear; Y – yes.

[84] Mean time after stroke was s. s. longer in the IG when compared to the CG.

[85] No concise description of primary/secondary outcomes, not all instruments are well described.

[86] IG: 15/16 (93.8%) // CG: 15/16 (93.8%).

[87] No reporting of the number of enrolled patients.

[88] IG: 99/99 (100%) // CG: 98/98 (100%); data from patients lost to follow-up was imputed.

[89] IG: 9/14 (64.4%) // CG: 12/15 (80%).

[90] IG: 15/15 (100%) // CG: 15/15 (100%).

[91] IG: 25/25 (100%) // CG: 24/24 (100%).

[92] Insufficient reporting on loss to f/u.

[93] No protocol available.

Table A-6: Risk of bias of RCTs for FES lower extremities identified by the update search (adapted version of the PEDRO risk of bias tool [81]) – part 3/3

First author, year	Morone, 2012 [169]	Sheffler, 2013/ 2015 [105, 106]	Tan, 2014 [170]	You, 2014 [171]	Zheng, 2018 [172]
1. Were participants randomly allocated (selection bias)?	U	U	Y	Y	Y
2. Was assessment performed blinded (detection bias)?	Y	Y	N	Y	Y
3. Allocation concealment (selection bias)?	U	Y	U	U	U
4. Prospective design?	Y	Y	Y	Y	Y
5. Clear definition of eligibility criteria?	Y	Y	Y	Y	N
6. Comparability of experimental and control groups at baseline?	N[94]	Y	Y	Y	Y
7. Clear definition and adequate assessment of study outcomes?	Y	Y	Y	Y	Y
8. Comparable treatment of randomized groups aside from investigated effects?	Y	U[95]	Y	Y	Y
9. Reporting of side effects?	N	N	N	N	N
10. Intention-to-treat analysis reported?	N	Y	Y	N	Y
11. (Almost) Complete outcome data (no attrition bias)?	U[95]	Y[96]	N[97]	Y[98]	Y[99]
12. No selective reporting (no reporting bias)?	U[100]	Y	U[100]	U[100]	U[101]
13. Adequate follow up assessment(s)?	N	Y	Y	Y	N
14. Do the results sufficiently support the conclusions reported?	Y	Y	N	N	N
Overall RoB (quality rating)	**High (-)**	**Moderate (+)**	**High (--)**	**High (-)**	**High (-)**
Evidence level	**2b**	**1b**	**2b**	**2b**	**2b**

Abbreviations: LoE – level of evidence; N – no; RoB – risk of bias; U – unclear; Y – yes.

[94] IG younger and more affected in comparison to CG.

[95] Insufficient reporting.

[96] No attrition at the end of treatment until 3 months post treatment. Relevant attrition at 6 months post treatment. No information on potential imputation of data.

[97] Although an ITT analysis has been used, no information on imputation of data was reported. IG1: 13/19 (68.8%) // IG2: 12/18 (66.7%) // CG: 12/18 (66.7%)

[98] IG: 19/21 (90.5%) // CG: 18/21 (85.7%)

[99] IG1: 18/20 (90%) // IG2: 15/20 (75%) // CG: 15/20 (75%)

[100] No study protocol available.

[101] Study protocol retrospectively registered.

Table A-7: Evidence profile: efficacy and safety of functional electrical stimulation for stroke rehabilitation

Quality assessment							Summary of findings			
							N of patients		Effect	Quality
N of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	FES + SoC	SoC alone		
N. peroneus FES										
Ability to walk										
1	RCT	not serious	not serious	not serious	serious[102]	none	54	56	Ø	Moderate
Walking speed										
2	RCT	not serious	not serious	not serious	serious[102]	none	70	72	Ø	Moderate
Gait distance, balance: NR										
Gait training with flexor reflex stimulation										
Ability to walk										
2	RCT	not serious	serious	not serious	serious[102]	none	33	31	Ø in 2 studies + for 40 m walk test in 1 study	Low
Walking speed										
2	RCT	not serious	not serious	not serious	serious[102]	none	33	31	+ in 2 studies	Moderate
Gait distance, balance: NR										
Multi-channel FES										
Ability to walk: NR										
Walking speed										
2	RCT	not serious	not serious	not serious	very serious[102 103]	none	38	35	ND in 1 study Ø in 1 study	Low
Gait distance										
1	RCT	not serious	not serious	not serious	very serious[102 103]	none	18	15	+	Low
Balacnce: NR										
Tilt sensor FES										
Ability to walk										
2	RCT	not serious	not serious	not serious	not serious	none	341	351	Ø	High

[102] Optimal information size not met.

[103] low statistical power to detect a difference.

Quality assessment							Summary of findings			
							N of patients		Effect	Quality
N of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	FES + SoC	SoC alone		
Walking speed										
2	RCT	not serious	not serious	not serious	not serious	none	341	351	Ø	High
Gait distance										
2	RCT	not serious	not serious	not serious	not serious	none	341	351	Ø	High
Balance										
2	RCT	not serious	serious	not serious	not serious	none	341	351	Ø in 2 studies (TUG) - in 1 studies (BBS)	Moderate
Electrostimulation of the peroneal nerve while walking with implanted System										
Walking speed										
1	RCT	not serious	not serious	not serious	very serious[102 103]	none	13	12	Ø	Low
Ability to walk, Gait distance, balacnce: NR										
multi-channel FES with percutaneous wire electrodes										
Ability to walk										
1	RCT	not serious	not serious	not serious	very serious[102 103]	none	16	16	ND	-
Gait distance										
1	RCT	not serious	not serious	not serious	very serious[102 103]	none	16	16	Ø	Low
Walking speed, balance: NR										
FES combined with electromechanical gait trainer										
Ability to walk										
2	RCT	not serious	not serious	not serious	serious[102]	Very serious[104]	31 31	31 32	FES +gait trainer vs. SoC alone: + FES + gait trainer vs. gait trainer alone: Ø	Very Low
Walking speed										
2	RCT	not serious	not serious	not serious	serious[102]	very serious[104]	31 31	31 32	FES +gait trainer vs. SoC alone: + FES + gait trainer vs. gait trainer alone: Ø	Very low
Gait distance: NR										
Balance										
2	RCT	not serious	not serious	not serious	serious[102]	very serious[104]	31 31	31 32	FES +gait trainer vs. SoC alone: Ø FES + gait trainer vs. gait trainer alone: Ø	Very low

[104] Duplicate publication bias strongly suspected.

Quality assessment							Summary of findings			
							N of patients		Effect	Quality
N of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	FES + SoC	SoC alone		
Mixed electrostimulation programs lower extremity (also while walking)										
Ability to walk										
1	RCT	not serious	not serious	serious[105]	very serious[102 103]	none	20	18	(+)[106]	Very low
Walking speed, gait distance, balance: NR										
Bike training (Cycling) with FES										
Ability to walk										
2	RCT	not serious	serious	serious[107]	serious[102]	none	41	39	Ø in 1 study + (FAC, POMA, PI) and Ø (FAC, POMA, FU) in 1 study	very low
Walking speed										
3	RCT	not serious	serious	serious[107]	serious[102]	none	46	44	Ø in 2 studies + in 1 study	very low
Gait distance, balance: NR										
Treadmill taining with FES										
Ability to walk: NR										
Walking speed										
1	RCT	not serious	not serious	not serious	very serious[102 103]	none	16	16	+	Low
Gait distance: NR										
Balance										
1	RCT	not serious	not serious	not serious	very serious[102 103]	none	16	16	+	Low

Comments: For inconsistency, a standardized judgement was not possible because no meta-analysis (incl. i-square) was conducted.
Based on the results of the individual studies, inconsistency was judged to be serious if they differed from each other (e.g., pointed in different directions).

Abbreviations: FES – functional electrical stimulation; N – number; RCT – randomised controlled trial; SoC – standard of care.

105 Insufficient description of intervention: it is unclear whether an electromechanical gait trainer was used additionally.

106 Significant group differences only for the differences of the FAC to the baseline measurement, not for absolute values.

107 Study sample also included patients with acquired other brain injuries.

Applicability table

Table A-8: Summary table characterising the applicability of a body of studies

Domain	Description of applicability of evidence
Population	No applicabiltiy concerns related to the population of interest were identified.
Intervention	Numerous different modalities of FES and robotic devices can be used in upper and lower limb stroke rehabilitation. The generalisability and applicability is limited hereby.
Comparators	All of the studies and reviews used standard rehabilitation as their comparator of interest. This included primarily physiotherapy and occupational therapy across all included studies. The comparators covered "standard rehabilitation", being heterogenous as well (e.g., RAR or FES in combination with other supportive tools such as a treadmill, cycling, etc.).
Outcomes	No applicability concerns were identified. Evidence was found for all outcomes of interest, although outcomes sometimes overlapped and numerous different outcome instruments are used within clinical trials.
Setting	For lower limb stroke rehabilitation, studies were conducted in the following settings for the evaluation of FES: inpatient setting (8/17 studies), outpatient setting (4/17 studies). One study reported that the study was undertaken in a rehabilitation clinic (without specifying whether it was an inpatient or outpatient stay) and the remaining studies (4/17) did not report sufficiently on the setting. For the evaluation of lower limb RAR, seven studies included stroke patients in the in-patient rehabilitation setting, the remaining three studies evaluated RAR in the outpatient setting. For upper limb stroke rehabilitation, the identified guideline did not report on the setting of the specific identified studies. The setting is a concern for applicability and a more specific evaluation needs to reflect the specific setting adequately.

List of ongoing randomised controlled trials

Table A-9: List of ongoing randomised controlled trials evaluating the clinical benefit of robot assisted stroke rehabilitation

Identifier/Trial name	Invervention	Comparison	Primary Outcomes	Type of Study	No of pts planned	Estimated study completion date	Sponsor
Lower limb stroke rehabilitation							
NCT03727919/TARGET	Exoskeleton-assisted gait training (Ekso GT)	Delayed Experimental Group No Interventio	■ Functional Ambulation Categories [Time Frame: 12 weeks post-stroke]	RCT	60	December 2021	Universiteit Antwerpen
NCT0398045	Indego Exoskeleton assisted gait training	Standard Rehabilitation	■ The Functional Independence Measure (FIM™) [Time Frame: Baseline (Day 1) and at 4-weeks to measure change] ■ The two minute walk tyest (2-MWT) [Time Frame: Baseline (Day 1) and at 4-weeks to measure change]	RCT	50	September 2024	University of Oklahoma
NCT04241848/POET	Powered Orthotic Exoskeleton Training Group (device: Keeogo)	Ambulation training alone	■ Five Times Sit to Stand Test (5xSTS) [Time Frame: Change from Baseline after completing 36 training sessions (approximately 3 months time)]	RCT	15	March 2022	VA Office of Research and Development
NCT03264235	Training with the Keeogo exoskeleton	Traditional Stair Training	■ Change in Timed Stair Climb Test speed from baseline [Time Frame: Initial Visit (Week 1); Post testing (Week 2)]	RCT	30	August 2020	Shirley Ryan AbilityLab
NCT04309305/RE-ASSIST	Training with EksoGT™ exoskeleton	Standard rehabilitation No intervention (healthy control)	■ Functional Independence Measure (FIM) ■ Within-brain functional connectivity ■ TMS recruitment curve slope ■ electroencephalogram (EEG) ■ electromyography (EMG) ■ 10MWT ■ 6MWT ■ TUG ■ Structural connectivity	RCT	75	August 2025	Kessler Foundation
NCT04173975	Training with wearable knee exoskeleton (BELK)	No intervention: training without exoskeleton	■ Change in walking velocity [Time Frame: Before and Immediately after the rehabilitation training of each arm (Initial, after 3 weeks and final)] ■ Change in Gait Profile Score [Time Frame: Before and Immediately after the rehabilitation training of each arm (Initial, after 3 weeks and final)]	Crossover RCT	15	August 2021	Casa di Cura Privata del Policlinico SpA

Identifier/Trial name	Invervention	Comparison	Primary Outcomes	Type of Study	No of pts planned	Estimated study completion date	Sponsor
NCT04087083	Traditional physical training and robotic training (G-EO system) in elderly stroke patients	Traditional physical training in elderly stroke patients	■ difference in falling risk between experimental arm and control arm [Time Frame: before treatment, at the end of rehabilitation sessions and 6 months, 12 months and 24 months after intervention]	RCT	150	September 2022	Istituto Nazionale di Ricovero e Cura per Anziani
KCT0004381	Gait Rehabilitation treatment using Healbot G	Gait Rehabilitation treatment using Treadmill	■ Functional near-infrared spectroscopy (timepoint: Before the first treatment, during the first and last (10^{th}) treatment)	RCT	30	August 2020	Asan Medical Center
KCT0004687	Walking training using the SUBAR exoskeleton	Traditional gait rehabilitation	■ 10 Meter Walk Test (timepoint: before and after the 10-treatment period)	RCT	34	May 2019	Cretem
KCT0003257	Training with Morning-walk robot	Conventional rehabilitation	■ functional Near-Infrared Spectroscopy (fNIRS)	RCT	60	January 2020	Asan Medical Center
KCT0005373	End-effector type lower limb rehabilitation robot plus 1.5 h of conventional physiotherapy	2h of conventional physiotherapy	■ Functional Ambulatory Category (time point: before and after treatment)	RCT	60	August 2021	Asan Medical Center
CTRI/2019/03/018100	Robotic Exoskeleton Assistive therapy for home based rehabilitation	Physiotherapy for rehabilitation	■ Clinical Scales of Rehabilitation: Modified Ashworth Scale, Brunnstorn Stage (timepoint: time of enrolment and at the end of the intervention) ■ Clinical NeuroPhyiological Signals: Electromyography changes; fMRI changes; Motor Evoked Potential Changes (timepoint: time of enrolment and at the end of the intervention)	RCT	20	2021	IIT Delhi IRD Unit (India)
CTRI/2020/05/024992	Robotic Exoskeleton Assistive therapy TMS integrated with Robotic exoskeleton device TMS therapy at hospital	Physiotherapy for rehabilitation	■ Clinical Scales of Rehabilitation: ■ Modified Ashworth Scale, ■ Brunnstorn Stage, ■ Electromyography changes, ■ Cortical Excitability, ■ Motor Evoked Potential Changes, ■ fMRI changes ■ All outcomes measured at the time of enrolment and at the end of the intervention	RCT	120	2023	Ministry of Defense (India)
Upper limb stroke rehabilitation							
NCT03571529	EMG-driven exoskeleton hand robot	Conventional physiotherapy	■ Fugl-Meyer Upper Extremity Assessment: [Time Frame: Change from pre-interventional Fugl-Meyer Upper Extremity score at the end of the 15 sessions intervention that will be performed 5 days in a week at a total of 3 weeks.]	RCT	40	May 2020	Bahçeşehir University

Identifier/Trial name	Invervention	Comparison	Primary Outcomes	Type of Study	No of pts planned	Estimated study completion date	Sponsor
NCT04201613/RESTORE	Robotic exoskeleton (KINARM) in different stages and intensities	Standard Rehabilitation	■ Change in Fugl-Meyer upper extremity motor function score (FMA) [Time Frame: From baseline to 44 days]	RCT	132	October 2023	University of Calgary
NCT04463888	Robot training with Smart Home-based Exoskeleton Robot System	Standard Rehabilitation (occupational therapy)	■ Change in the result of Box and blocks test [Time Frame: baseline, 4 weeks and 16 weeks]	Crossover RCT	44	December 2021	National Cheng-Kung University Hospital
NCT02770300	Arm Light Exoskeleton Rehab Station (ALEx RS)	Conventional therapy	■ Safety evaluated through the number of adverse events [Time Frame: 2 years] ■ Efficacy evaluated through Fugl-Meyer [Time Frame: 2 years]	RCT	48	December 2020	Wearable Robotics srl.
NCT03888326	Robotic Rehabilitation (KINARM) plus 1x1 anodal tDCS Robotic Rehabilitation plus sham tDCS	Standard rehabilitation Rehabilitation	■ Robotic limb position matching standardized score [Time Frame: Baseline, Within 1 week of completing the 10 day intervention and 3-month follow-up] ■ Robotic kinaesthesia standardized score [Time Frame: Baseline, Within 1 week of completing the 10 day intervention and 3-month follow-up]	RCT	30	August 2020	University of Calgary
NCT04484571	Training with NEEM robotic elbow exoskeleton	Conventional rehabilitation	■ Change in the score of the upper-extremity section of Fugl-Meyer assessment scale (FM 0-66) higher score means better [Time Frame: before and within 1 week after 4 weeks of treatment] ■ Change in the score of Modified Ashworth Scale (MAS 0-5 scoring 1+ as 2 for statistical analysis) higher score means worse [Time Frame: Before and within 1 week after 4 weeks of treatment]	RCT	60	July 2022	Azienda USL Toscana Nord Ovest
NCT03171649	Training with the Retrainer-S1 (combination of exoskeleton and FES)	Conventional therapy	■ Action Research Arm Test [Time Frame: 9 weeks]	RCT	68	May 2018	Villa Beretta Rehabilitation Center
ACTRN12618001132235	virtual myoelectric exoskeleton involving active assisted upper limb movements in virtual reality environment active upper limb movementsin mirror box	Conventional therapy	■ Muscle activation amplitude of deltoid during upper limb movements described in the Fugl Meyer scale	RCT	24	NR	Basque Country Government (Spain)
TCTR20200301001	Exoskeleton assisted upper limb training	Conventional training	■ Oxyhemoglobin in region of interest	RCT	63	August 2020	CUREs robotic

Identifier/Trial name	Invervention	Comparison	Primary Outcomes	Type of Study	No of pts planned	Estimated study completion date	Sponsor
TCTR20161220001	Occupational therapy and training with the Chulalongkorn University Rehabilitation robotic Exoskeleton system (CURE)	Conventional occupational therapy	■ Motor power (MRC scale) ■ Wolf Motor Function Test ■ Fugl-Meyer Assessment- upper extremity section ■ Spasticity using Modified Ashworth scale ■ Barthel ADL Index	RCT	76	July 2017	Higher Education Research Promotion National Research University (Thailand)
ChiCTR2000029506	Physical therapy, occupational therapy and New hand function rehabilitation training using an exoskeleton robot and mixed reality technique	Physical therapy, occupational therapy and unmirrored training	■ FIM (timepoint: 1 day before the training, the day after the training, 2 weeks after the training, 4 weeks after the training) ■ Mini mental state examination (timepoint: 1 day before the training, the day after the training, 2 weeks after the training, 4 weeks after the training)	RCT	18	December 2023	PLA General Hospital, Bejing (China)

Table A-10: List of ongoing randomised controlled trials evaluating the clinical benefit of functional electrical stimulation for stroke rehabilitation

	Invervention	Comparison	Primary Outcomes	Type of Study	N of pts planned	Estimated study completion date	Sponsor
Lower limb stroke rehabilitation							
NCT02797886	FES is applied in concert with the subject's volitional movement (VOL)	VOL	■ Voluntary Dorsiflexion, ■ Time to Complete 10 Meter Walk, ■ Center of Pressure of Plantar Loading During Walking Trial, ■ Joint Angles During Walking Trial, ■ Amplitude of the Major Components of Somatosensory Evoked Potentials, ■ Amplitude of the P40-N50 Complex During Movement Related Cortical Potentials, ■ Amplitude and Latency of M-Wave Component of EMG During Maximal Voluntary Contraction	RCT	45	June 2017	Kessler Foundation
NCT01876030	FES (Mygait)	Conventional gait re-education with or without AFO fitting	■ Change in velocity of gait ■ Change in step length	RCT	40	June 2017	Hadassah Medical Organization
ChiCTR-INR-17012441	FES	■ Normal walking ■ Placebo stimulus	■ modified barthel index ■ Three dimension gait analysis	RCT	60	NR	Sun Yat-sen Memorial Hospital, Sun Yat-sen University (China)
UMIN000020604/NCT02898168 RALLY	Gait training with FES + conventional rehabilitation therapy	Gait training without FES + conventional rehabilitation therapy	■ 6-minute walk test at baseline and ater 8-week intervention	RCT	200	November 2019	Kagoshima University
Upper limb stroke rehabilitation							
NCT04014270	Self-modulated functional electrical stimulation	Standard rehabilitation	■ Change in the motor part of the Fugl-Meyer Assessment of the Upper Extremity (FMA-UE) scale, calculated from baseline to post-intervention (2 weeks)	RCT	80	September 30, 2021	Intento SA
ACTRN12618000344291	FES + music therapy and standard rehabilitation	Standard rehabilitation alone	■ Motor Assessment Scale, using the upper limb items (UL-MAS). ■ Manual Muscle Tests of the upper limb (MMT-UL) ■ 9-Hole-Peg test (9HPT)	RCT	40	NR	University of Melbourne

Literature search strategies robot assisted rehabilitation

Search strategy for Cochrane

Search Name: Robot assisted rehabilitation	
Last Saved: 07/05/2020 18:03:08	
ID	Search
#1	MeSH descriptor: [Stroke] explode all trees
#2	(stroke*) (Word variations have been searched)
#3	MeSH descriptor: [Paresis] explode all trees
#4	(Hemipare*) (Word variations have been searched)
#5	(Haemipare*) (Word variations have been searched)
#6	(Hemi-pare*) (Word variations have been searched)
#7	(Haemi-pare*) (Word variations have been searched)
#8	MeSH descriptor: [Hemiplegia] explode all trees
#9	(Hemiplegi*) (Word variations have been searched)
#10	(Haemiplegi*) (Word variations have been searched)
#11	(Hemi-plegi*) (Word variations have been searched)
#12	(Haemi-plegi*) (Word variations have been searched)
#13	MeSH descriptor: [Upper Extremity] explode all trees
#14	MeSH descriptor: [Lower Extremity] explode all trees
#15	((upper OR low*) NEAR (extremity OR extremities OR limb*)) (Word variations have been searched)
#16	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 (Word variations have been searched)
#17	MeSH descriptor: [Exoskeleton Device] explode all trees
#18	(exoskeleton*) (Word variations have been searched)
#19	(exo-skeleton*) (Word variations have been searched)
#20	(electromechanic*) (Word variations have been searched)
#21	(electro-mechanic*) (Word variations have been searched)
#22	(end-effector*) (Word variations have been searched)
#23	(endeffector*) (Word variations have been searched)
#24	(robot* NEAR effector*) (Word variations have been searched)
#25	(HAL):ti,ab,kw (Word variations have been searched)
#26	(Rex):ti,ab,kw (Word variations have been searched)
#27	#17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26
#28	MeSH descriptor: [Rehabilitation] explode all trees
#29	(Reha*) (Word variations have been searched)
#30	#28 OR #29 (Word variations have been searched)
#31	#27 AND #30 (Word variations have been searched)
#32	#16 AND #31
#33	(rehab* NEAR (exoskeleton* OR exo-skeleton* OR electromechanic* OR electro-mechanic* OR end-effector* OR endeffector* OR effector*)) (Word variations have been searched)
#34	(Ekso):ti,ab,kw (Word variations have been searched)
#35	(ReWalk):ti,ab,kw (Word variations have been searched)
#36	(Indego):ti,ab,kw (Word variations have been searched)
#37	(Armeo):ti,ab,kw (Word variations have been searched)
#38	(T-WREX):ti,ab,kw (Word variations have been searched)
#39	#32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38
Total hits: 310	

Search strategy for CRD

Search date: 07.05.2020	
ID	Search
1	MeSH DESCRIPTOR Exoskeleton Device EXPLODE ALL TREES
2	(exoskeleton*)
3	(exo-skeleton*)
4	(electromechanic*)
5	(electro-mechanic*)
6	(end-effector*)
7	(endeffector*)
8	(robot* NEAR effector*)
9	(ReWalk)
10	(Indego*)
11	(Ekso*)
12	(Armeo*)
13	(T-WREX)
14	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13
Total hits: 17	

Search strategy for Embase

Search date: 07.05.2020		
No.	Query Results	Results
#37.	#16 AND #36	776
#36.	#34 OR #35	1,008
#35.	'exoskeleton rehabilitation'/mj	378
#34.	#32 AND #33	730
#33.	rehabilitation:lnk	158,065
#32.	#17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31	14,257
#31.	't wrex':dn	3
#30.	armeo:dn	30
#29.	indego:dn	17
#28.	rewalk:dn	32
#27.	ekso:dn	24
#26.	rex:dn	134
#25.	hal:dn	30
#24.	(robot* NEAR/4 effector*):ti,ab,kw,de	243
#23.	'endeffector*':ti,ab,de,kw	51
#22.	'end-effector*':ti,ab,de,kw	966
#21.	'electro-mechanic*':ti,ab,kw,de	1,508
#20.	electromechanic*:ti,ab,kw,de	7,786
#19.	'exo-skeleton*':ti,ab,de,kw	17
#18.	exoskeleton*:ti,ab,de,kw	3,807
#17.	'exoskeleton (rehabilitation)'/exp	1,638
#16.	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15	1,283,973
#15.	((upper OR low*) NEAR/1 (extremity OR extremities OR limb*)):ti,ab,kw,de	206,596

#14.	'lower limb'/exp	415,609
#13.	'upper limb'/exp	308,617
#12.	'haemi-plegi*':ti,ab,de,kw	0
#11.	'hemi-plegi*':ti,ab,de,kw	19
#10.	haemiplegi*:ti,ab,de,kw	28
#9.	hemiplegi*:ti,ab,de,kw	25,108
#8.	'hemiplegia'/exp	20,030
#7.	'haemi-pare*':ti,ab,kw,de	0
#6.	'hemi-pare*':ti,ab,kw,de	152
#5.	haemipare*:ti,ab,kw,de	30
#4.	hemipare*:ti,ab,kw,de	28,524
#3.	'hemiparesis'/exp	22,421
#2.	stroke*:ti,ab,de,kw	413,658
#1.	'cerebrovascular accident'/exp	324,716

Search strategy for Medline

Search date: 07.05.2020	
ID	Search
1	exp Stroke/ (165561)
2	stroke*.mp. (354777)
3	exp Paresis/ (9191)
4	H?emipare*.mp. (13543)
5	H?emi-pare*.mp. (56)
6	exp Hemiplegia/ (12088)
7	H?emiplegi*.mp. (18740)
8	H?emi-plegi*.mp. (3)
9	exp Upper Extremity/ (184838)
10	exp Lower Extremity/ (185056)
11	((upper or low*) adj2 (extremity or extremities or limb*)).mp. (174985)
12	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 (837006)
13	exp Exoskeleton Device/ (1145)
14	exoskeleton*.mp. (4088)
15	exo-skeleton*.mp. (10)
16	electromechanic*.mp. (7646)
17	electro-mechanic*.mp. (1639)
18	end-effector*.mp. (978)
19	endeffector*.mp. (8)
20	(robot* adj5 effector*).mp. (263)
21	HAL.ti,ab. (2152)
22	Rex.ti,ab. (2272)
23	13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 (18497)
24	exp Rehabilitation/ (353120)
25	rehabilitation.fs. (221945)
26	24 or 25 (503167)
27	23 and 26 (1460)
28	12 and 27 (1000)

29	(rehab* adj5 (exoskeleton* or exo-skeleton* or electromechanic* or electro-mechanic* or end-effector* or endeffector* or effector*)).mp. (359)
30	Ekso GT.mp. (4)
31	ReWalk.mp. (31)
32	Indego.mp. (11)
33	Armeo.mp. (58)
34	T-WREX.mp. (3)
35	28 or 29 or 30 or 31 or 32 or 33 or 34 (1274)
36	remove duplicates from 35 (839)

Search strategy for PEDro

Date of Search: 20.05.2020
Searchstring (Advanced Search Mode): exoskelet* AND stroke* in Title/Abstract
Total hits: 20

Literature search strategies functional electrical stimulation for stroke rehabilitation

Expanded Medline search including further electric stimulation interventions in addition to FEST was conducted in July (the approach applied in Medline was adapted in all databases used in the original search – the detailed strategies are available on request).

Search strategy for Cochrane

Search Name: Stroke Rehabilitation with FEST	
Last Saved: 18/05/2020 18:25:28	
Comment: GG/MW 180520	
ID	Search
#1	MeSH descriptor: [Stroke] explode all trees
#2	(stroke*) (Word variations have been searched)
#3	MeSH descriptor: [Paresis] explode all trees
#4	(Hemipare*) (Word variations have been searched)
#5	(Haemipare*) (Word variations have been searched)
#6	(Hemi-pare*) (Word variations have been searched)
#7	(Haemi-pare*) (Word variations have been searched)
#8	MeSH descriptor: [Hemiplegia] explode all trees
#9	(Hemiplegi*) (Word variations have been searched)
#10	(Haemiplegi*) (Word variations have been searched)
#11	(Hemi-plegi*) (Word variations have been searched)
#12	(Haemi-plegi*) (Word variations have been searched)
#13	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12
#14	MeSH descriptor: [Upper Extremity] explode all trees
#15	MeSH descriptor: [Lower Extremity] explode all trees
#16	((upper OR low*) NEAR (extremity OR extremities OR limb*)) (Word variations have been searched)

#17	#14 OR #15 OR #16 (Word variations have been searched)
#18	#13 AND #17 (Word variations have been searched)
#19	("functional electric* stimul*") (Word variations have been searched)
#20	("functional electrostimul*") (Word variations have been searched)
#21	("functional electro-stimul*") (Word variations have been searched)
#22	(FES):ti,ab,kw (Word variations have been searched)
#23	(FEST):ti,ab,kw (Word variations have been searched)
#24	MeSH descriptor: [Electric Stimulation Therapy] explode all trees
#25	(functional)
#26	#24 AND #25 (Word variations have been searched)
#27	#19 OR #20 OR #21 OR #22 OR #23 OR #26 (Word variations have been searched)
#28	MeSH descriptor: [Stroke Rehabilitation] explode all trees
#29	(rehab*) (Word variations have been searched)
#30	#28 OR #29 (Word variations have been searched)
#31	#27 AND #30 (Word variations have been searched)
#32	(rehab* NEAR ("functional electric* stimul*" OR "functional electrostimul*" OR "functional electrostimul*")) (Word variations have been searched)
#33	#31 OR #32 (Word variations have been searched)
#34	#18 AND #33 (Word variations have been searched)
#35	(MyndMove) (Word variations have been searched)
#36	(myndtec) (Word variations have been searched)
#37	(WalkAide) (Word variations have been searched)
#38	(Odstock) (Word variations have been searched)
#39	(innovative neurotronic*) (Word variations have been searched)
#40	#34 OR #35 OR #36 OR #37 OR #38 OR #39 (Word variations have been searched)
Total hits: 374	

Search strategy for CRD

Search Name: Stroke Rehabilitation with FEST (GG/MW 180520)	
Search date: 18.05.2020	
ID	Search
1	MeSH DESCRIPTOR Stroke EXPLODE ALL TREES
2	(Stroke*)
3	MeSH DESCRIPTOR Paresis EXPLODE ALL TREES
4	(Hemipare*)
5	(Haemipare*)
6	(Hemi-pare*)
7	(Haemi-pare*)
8	MeSH DESCRIPTOR Hemiplegia EXPLODE ALL TREES
9	(Hemiplegi*)
10	(Haemiplegi*)
11	MeSH DESCRIPTOR Upper Extremity EXPLODE ALL TREES
12	MeSH DESCRIPTOR Lower Extremity EXPLODE ALL TREES
13	((upper OR low*) NEAR (extremity OR extremities OR limb*))
14	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13
15	(functional electric* stimul*)

16	(functional electrostimul*)
17	(functional electro-stimul*)
18	(FES)
19	(FEST)
20	(Electric Stimulation Therapy)
21	(functional)
22	#20 AND #21
23	#15 OR #16 OR #17 OR #18 OR #19 OR #22
24	#14 AND #23
25	(MyndMove)
26	(myndtec)
27	(WalkAide)
28	(Odstock)
29	(innovative neurotronic*)
30	#24 OR #25 OR #26 OR #27 OR #28 OR #29
Total hits: 36	

Search strategy for Embase

Search date: 19.05.2020		
#35.	#28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34	698
#34.	'innovative neurotronic*':df	11
#33.	odstock:df	9
#32.	n.i:dn	0
#31.	walkaide:dn	29
#30.	myndtec:df	0
#29.	myndmove:dn	0
#28.	#18 AND #27	672
#27.	#25 OR #26	9,247
#26.	(rehab* NEAR/4 ('functional electric* stimul*' OR 'functional electrostimul*' OR 'functional electrostimul*' OR fes OR fest)):ti,ab,de,kw	240
#25.	#19 OR #20 OR #21 OR #22 OR #23 OR #24	9,247
#24.	fest:ti,ab	113
#23.	fes:ti,ab	7,077
#22.	'functional electro-stimul*':ti,ab,de,kw	7
#21.	'functional electrostimul*':ti,ab,de,kw	93
#20.	'functional electric* stimul*':ti,ab,de,kw	4,034
#19.	'functional electrical stimulation'/exp	2,078
#18.	#13 AND #17	27,673
#17.	#14 OR #15 OR #16	779,421
#16.	((upper OR low*) NEAR/1 (extremity OR extremities OR limb*)):ti,ab,kw,de	207,007
#15.	'lower limb'/exp	416,302
#14.	'upper limb'/exp	309,041
#13.	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12	534,100
#12.	'haemi-plegi*':ti,ab,de,kw	0
#11.	'hemi-plegi*':ti,ab,de,kw	19
#10.	haemiplegi*:ti,ab,de,kw	28

#9.	hemiplegi*:ti,ab,de,kw	25,108
#8.	'hemiplegia'/exp	20,030
#7.	'haemi-pare*':ti,ab,kw,de	0
#6.	'hemi-pare*':ti,ab,kw,de	152
#5.	haemipare*:ti,ab,kw,de	30
#4.	hemipare*:ti,ab,kw,de	28,524
#3.	'hemiparesis'/exp	22,421
#2.	stroke*:ti,ab,de,kw	413,658
#1.	'cerebrovascular accident'/exp	324,716

Search strategy for Medline

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily <2016 to May 14, 2020>, Ovid MEDLINE(R) <1946 to May Week 2 2020>	
Search date: 02.07.2020	
ID	Search
1	exp Stroke/ (165986)
2	stroke*.mp. (355831)
3	exp Paresis/ (9211)
4	H?emipare*.mp. (13567)
5	H?emi-pare*.mp. (56)
6	exp Hemiplegia/ (12093)
7	H?emiplegi*.mp. (18764)
8	H?emi-plegi*.mp. (3)
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 (402684)
10	exp Upper Extremity/ (185106)
11	exp Lower Extremity/ (185247)
12	((upper or low*) adj2 (extremity or extremities or limb*)).mp. (175391)
13	10 or 11 or 12 (454285)
14	9 and 13 (18181)
15	functional electric* stimul*.mp. (2942)
16	functional electrostimul*.mp. (72)
17	functional electro-stimul*.mp. (5)
18	FES.ti,ab. (6122)
19	FEST.ti,ab. (151)
20	exp Electric Stimulation Therapy/ (93179)
21	functional.mp. (1499897)
22	20 and 21 (9400)
23	15 or 16 or 17 or 18 or 19 or 22 (15345)
24	rehabilitation.fs. (222580)
25	exp Stroke Rehabilitation/ (17071)
26	24 or 25 (234003)
27	23 and 26 (2238)
28	(rehab* adj5 (functional electric* stimul* or functional electrostimul* or functional electrostimul*)).mp. (141)
29	27 or 28 (2292)
30	14 and 29 (546)
31	MyndMove.mp. (0)

32	myndtec.mp. (0)
33	WalkAide.mp. (9)
34	Odstock.mp. (24)
35	innovative neurotronic*.mp. (0)
36	30 or 31 or 32 or 33 or 34 or 35 (575)
37	remove duplicates from 36 (454)
Expanded Medline search from July 2020 (the approach applied in Medline was adapted in all databases used in the original search – the detailed strategies are available on request): Database: Ovid MEDLINE(R) and In-Process & Other Non-Indexed Citations and Daily <1946 to June 30, 2020>, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily <2016 to June 30, 2020>	
Search date: 02.07.2020	
ID	Search
1	exp Stroke/ (168701)
2	stroke*.mp. (393405)
3	exp Paresis/ (9275)
4	H?emipare*.mp. (15015)
5	H?emi-pare*.mp. (69)
6	exp Hemiplegia/ (12136)
7	H?emiplegi*.mp. (20241)
8	H?emi-plegi*.mp. (3)
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 (441964)
10	exp Upper Extremity/ (186472)
11	exp Lower Extremity/ (186603)
12	((upper or low*) adj2 (extremity or extremities or limb*)).mp. (196566)
13	10 or 11 or 12 (477251)
14	9 and 13 (19966)
15	functional electric* stimul*.mp. (3375)
16	functional electrostimul*.mp. (80)
17	functional electro-stimul*.mp. (5)
18	FES.ti,ab. (7130)
19	FEST.ti,ab. (188)
20	exp Electric Stimulation Therapy/ (94213)
21	functional.mp. (1709560)
22	20 and 21 (9540)
23	15 or 16 or 17 or 18 or 19 or 22 (16682)
24	rehabilitation.fs. (224587)
25	exp Stroke Rehabilitation/ (17380)
26	24 or 25 (236235)
27	23 and 26 (2271)
28	(rehab* adj5 (functional electric* stimul* or functional electrostimul* or functional electrostimul*)).mp. (171)
29	27 or 28 (2353)
30	14 and 29 (559)
31	MyndMove.mp. (0)
32	myndtec.mp. (0)
33	WalkAide.mp. (13)
34	Odstock.mp. (29)
35	innovative neurotronic*.mp. (0)
36	30 or 31 or 32 or 33 or 34 or 35 (596)
37	remove duplicates from 36 (459)

38	(low* adj2 (extremity or extremities or limb*)).mp. (140130)
39	11 or 38 (279101)
40	9 and 39 (8470)
41	(electric* stimul* or electrostimul* or electro-stimul*).mp. (171037)
42	(Electric* adj5 Stimul*).mp. (182180)
43	41 or 42 (183828)
44	"Therapeutic Use".fs. (2527748)
45	(therap* or treat* or program* or interven* or regimen*).mp. (12608472)
46	44 or 45 (12608472)
47	43 and 46 (62676)
48	20 or 47 (127383)
49	EST.ti,ab. (24035)
50	tENS.ti,ab. (23127)
51	electr* acupuncture*.mp. (1279)
52	electroacupuncture*.mp. (7261)
53	electro-acupuncture*.mp. (1026)
54	48 or 49 or 50 or 51 or 52 or 53 (174472)
55	26 and 54 (5652)
56	(rehab* adj5 (electric* stimul* or electrostimul* or electro-stimul*)).mp. (542)
57	54 and 56 (474)
58	55 or 57 (5891)
59	40 and 58 (308)
60	limit 59 to dt=20120625-20200702 (186)
61	remove duplicates from 60 (114)
62	61 not 37 (45)

Search strategy for PEDro

Date of Search: 20.05.2020
Searchstring (Advanced Search Mode): FES* AND stroke* in Title/Abstract
Total hits: 87

HTA Austria
Austrian Institute for
Health Technology Assessment
GmbH