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High-dose high-intensity Queen Square upper-limb rehabilitation for people with chronic stroke (INTENSIVE): protocol for a single-centre, randomised controlled trial

Lisa Tedesco Triccas ,[1,2] Sebastian Sporn,[1] Mireia Coll I Omana,[1] Fran Brander,[3] Kate Kelly,[3] Sven Bestmann,[1] Nick Ward[1,3]

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[1]Department of Clinical and Movement Neurosciences, UCL Queen Square Institute of Neurology, London, UK
[2]Faculty of Rehabilitation Sciences, REVAL Rehabilitation Research Center, Hasselt University, Hasselt, Belgium
[3]University College London Hospitals NHS Foundation Trust National Hospital for Neurology and Neurosurgery, London, UK

Correspondence to
Dr Lisa Tedesco Triccas; l.triccas@ucl.ac.uk

ABSTRACT

Introduction There is currently insufficient high-quality evidence to make general recommendations about high-dose high-intensity upper-limb rehabilitation programmes. Here we describe a randomised controlled trial that will determine the efficacy of two forms of high-dose, high-intensity upper-limb rehabilitation provided in a rehabilitation unit setting.

Methods and analysis Patients with moderate upper-limb impairment (n=105, at least 6 months after stroke) will be randomised to either (1) high-dose high-intensity conventional upper-limb rehabilitation, (2) high-dose high-intensity virtual reality-based upper-limb rehabilitation and (3) usual care (a waiting list control group). Groups 1 and 2 will receive a minimum of 45 hours of active time on task over 3 weeks. Outcome measures will be collected at (T1) baseline; (T2) immediately post intervention and (T3) 3 months after the intervention has finished. The primary outcome measure will be the Fugl-Meyer Upper Extremity Assessment at 3 months after the intervention. Secondary outcome measures will be clinical, kinematic and neurophysiological using transcranial magnetic stimulation and electroencephalography. Explanatory measures will include MRI-based markers for integrity of the corticospinal tract, dorsal column-medial lemniscal pathway, grey and white matter and lesion load. The aim is to detect a difference of 7.25 points on the Fugl-Meyer Upper Extremity Assessment between each treatment group and the waitlist control group, with a power of 0.9 and significance of 0.025 (to account for two primary analyses). Analysis of change in the primary and secondary outcome measures will be performed using mulitple regression analysis.

Ethics and dissemination The study protocol (V.1) has been approved by the Wales Research Ethics Committee 2 Cardiff (Rec reference: 22/WA/0065) on 15 March 2022. All recruited participants will provide informed consent. Trial results will be disseminated through peer-reviewed publications, presentations at major stroke/neurorehabilitation conferences and outreach to relevant stakeholder communities.

Trial registration number NCT05527262.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This single-site single-blinded randomised controlled trial will investigate genuinely high-dose high-intensity upper-limb rehabilitation delivered in two distinct ways.
⇒ Outcomes are assessed using clinical, kinematic and neurophysiological measures collected at baseline and post intervention, and clinical and kinematic measures at three-month follow-up, as recommended by the International Stroke Recovery and Rehabilitation Alliance.
⇒ Assessors of clinical but not kinematic or neurophysiological outcome measures are blind to treatment allocation.

INTRODUCTION AND RATIONALE

Stroke is the primary neurological cause of disability globally.[1] Beyond the first few hours, the consequences of stroke are treated through the process of neurorehabilitation. Many patients in the UK find it difficult to access rehabilitation services once 6 months have passed since their stroke. This is partly related to a belief that most meaningful recovery happens within 6 months.[2] However, the UK National Clinical Guidelines (UKNCG) for stroke now recommend that rehabilitation should be needs-led not time-led. One of the major contributors to ongoing physical disability is persistent difficulty in using the affected upper limb.[3] There have been some attempts to provide patients with high-dose, high-intensity upper-limb rehabilitation in the chronic stage (beyond 6 months) of stroke.[4–6] However, the UKNCG argue that there is insufficient high-quality evidence to make general recommendations regarding the provision of such programmes and that improving the evidence base for

intensive upper-limb rehabilitation programmes in chronic stroke is a high priority.

Intensive upper-limb rehabilitation can be delivered using conventional treatment or technology-based (eg, virtual reality (VR), robotics) treatment. The Queen Square upper-limb neurorehabilitation programme (QSUL) uses predominantly conventional physiotherapy and occupational therapy, providing 90 hours of timetabled treatment over 3 weeks.[6] QSUL leads to clinically meaningful upper-limb improvements that are maintained for at least 6 months,[6] but this has not been corroborated in a randomised controlled trial (RCT). There are numerous examples of VR and robotics being used to treat poststroke upper-limb movement impairment. One novel example is an exergame that uses semi-immersive VR alongside deweighting of the arm. This system aims to encourage high-dose high-intensity exploratory arm movements, focusing on movement quality in a rewarding game-based environment.[7] A preliminary study with 24 patients with subacute stroke compared this upper-limb VR-based neuroanimation therapy and conventional occupational therapy with a historical control group, found both active treatments to be equally effective in promoting changes in upper-limb activity.[7] In general, however, high-quality evidence of efficacy for VR-based upper-limb treatments is lacking, particularly in chronic stroke, perhaps due to the low dose of the treatment programmes. The dose of neurorehabilitation that people with stroke can undertake is often underestimated.[8]

The purpose of this RCT is to provide high-quality evidence on the efficacy of high-dose high-intensity upper-limb rehabilitation compared with usual care in patients with chronic stroke. High-dose upper-limb rehabilitation will consist of maximal 90 hours of available treatment time (minimum 45 hours' time-on-task) over 3 weeks with follow-up at 3 months. Treatment will be delivered using either conventional or VR-based treatment. The conventional treatment will be in the form of the QSUL programme,[6] while the VR-based treatment will be delivered using a semi-immersive neuroanimation exergame.[7] Each high-dose high-intensity treatment will be compared with usual care using a range of clinical, kinematic and neurophysiological measures as recommended by recent Stroke Recovery and Rehabilitation Roundtable (SRRR) consensus papers.[9 10]

The primary outcome measure will be the Fugl-Meyer Upper Extremity Assessment (FMUE). We will also determine changes in a number of secondary clinical scores, as well as kinematic and neurophysiological measures (presence and absence of Transranial Magnetic Stimulation (TMS) motor/Electroencephalography (EEG) sensory-evoked potentials (MEP/SEP+/-), MEP amplitude, N20/P25 SEP amplitude, EEG resting-state functional connectivity. Baseline neurophysiological and neuroimaging assessments using Magnetic Resonance Imaging (MRI) of stroke-related damage may also be useful in explaining differences in the treatment response.[11]

The primary objectives are to determine:

1. Whether QSUL is more effective at reducing impairment in patients with chronic stroke than usual care.
2. Whether high-dose VR-based rehabilitation treatment is more effective at reducing impairment in patients with chronic stroke than usual care.

The main hypothesis for this research is that QSUL/VR-based rehabilitation treatment is more effective at reducing impairment than usual care for people with chronic stroke.[6]

The secondary objectives are to explore:

1. Whether QSUL and VR-based rehabilitation treatments are *equivalent* for both primary and secondary outcome measures.
2. Whether QSUL and VR-based rehabilitation treatments have *differential effects* on impairment, activity and participation outcomes.
3. Whether the effect of high-dose upper-limb rehabilitation treatment depends on pretreatment clinical, physiological and/or neuroanatomical phenotypes.

METHODS

Design

We will conduct a parallel single-site randomised, assessor-blind, stratified, controlled phase IIb clinical trial, including 105 chronic stroke survivors with upper-limb impairment. The protocol has been registered on the Clinical Trials registry (NCT05527262). The start date of the trial was 1 June 2022 and planned end date will be 30 September 2025 with recruitment dates from 15 June 2022 to 1 March 2025.

Patient population

Participants will be recruited from the University College London Hospital NHS Foundation Trust, specifically the National Hospital for Neurology and Neurosurgery, Queen Square. People with stroke will be initially screened and approached in the QSUL clinic where 300–400 patients/year are assessed by a consultant neurologist, physiotherapist and occupational therapist. Participants will be asked if they would like to take part in the study, and if they are interested, then they will be screened on the inclusion and exclusion criteria and provided with an information sheet.

Participants will be recruited using the following inclusion criteria: (1) a first-ever unilateral stroke (ischaemic or haemorrhagic) as defined by the WHO at least 6 months previously; (2) moderate upper-limb impairment as defined by an FMUE score between 19 and 46[12] (with passive shoulder flexion to 90°) and (3) must be able to voluntarily extend the thumb and/or two or more fingers of the affected hand (10° or more).[13] Exclusion criteria will be (1) other neurological diagnoses that interferes with the protocol; (2) serious communication, cognitive and language deficits (<7 on shortened version Montreal Cognitive Assessment or <34 on Cognitive Assessment Scale for patients with stroke)[14 15]; (3) frozen shoulder with severe shoulder pain measured by Chedoke Impairment

Inventory: Stage of Shoulder Pain 1, 2 and 3[16]; (4) increased tone in wrist/finger extensors (≥3 on Modified Ashworth Scale)[17]; (5) fatigue of <30 on the Functional Assessment of Chronic Illness Therapy Fatigue Scale[18]; (6) apraxia score of <5 on the TULIA assessment[19] and (7) vision impairment that impedes seeing the television screen for VR-based treatment.

Patient and public involvement

We conducted focus groups prior to the start of the trial, with purposively sampled stroke survivors and carers who had participated in the QSUL programme. Overall, the QSUL programme was viewed very positively as a neurorehabilitation intervention.[20] Follow-up questions concerned the design of a randomised clinical trial. The overall view was that randomisation to a waiting list as a control group was acceptable, but only if (1) the 'follow-up' period was limited to 3 months rather than the current 6 months and (2) treatment on the programme (if clinically indicated) should immediately follow the waiting list control period. Members of the focus groups were also asked about the acceptability of extra testing (kinematics, MRI, EEG, TMS). The group understood why these tests were needed but felt that the MRI, EEG and TMS measures should be performed prior to the QSUL programme not during it so as not to use up treatment time. Additionally, it was felt that transport would need to be provided on research days, just as it is for treatment days on QSUL currently.

Determination of sample size

The aim is to detect a difference of 7.25 points on the FMUE (minimum clinically important difference for FMUE is between 4.25 and 7.25)[12] between each treatment group and the waitlist control group with a power of 0.9 and significance of 0.025 (to account for two primary analyses). From the published QSUL data,[6] the SD of baseline FMUE in the target group (baseline FMUE 19–46) was 7.6. If we assume a 20% dropout, 35 per group will be required in each group.

Screening and minimisation procedures

Participants who agree to join the study will be asked to provide written informed consent (online supplemental appendix A) and will undergo an additional face-to-face screening session by one/two neurological physiotherapists at the Department of Clinical and Movement Neurosciences, Institute of Neurology, University College London. Treatment allocation will be conducted by an independent researcher by minimisation, which guarantees balance of upper-limb severity severe-to-moderate impairment (FMUE score 19–32: moderate to mild; FMUE score 33–46[12] and MEP+/- within each group).[21 22] Participants will be assigned to treatment groups or waitlist control through a unique identifier for use in the trial password-protected database. Clinical assessments will be scored by blinded assessors, but blinding to group allocation during the experiment could not be performed as main research staff will be providing the actual treatment (QSUL and VR). Study staff will be responsible for data entry, with the principal investigator verifying its accuracy. For participants who withdraw from the study, standard care will be continued.

Intervention

Participants will be allocated by an independent allocator to one of the three groups (figure 1): (1) conventional treatment, (2) VR-based treatment and (3) waitlist control receiving usual care. The intervention procedure will be conducted by trained healthcare professionals. See online supplemental appendix for a full description of conventional and VR-based treatments.

The Queen Square upper-limb neurorehabilitation programme

Participants have a 90-hour timetable over 3 weeks, 5 days a week. Our previous observations were that patients spend on average 45 hours of time on task (upper limb). The remaining time involves assessments (days 1 and 15), session preparation, within and between session rest, cardiovascular fitness, gait training (as it pertains to upper-limb function), trunk/core strengthening and education (promoting self-efficacy) (refer to the Template for

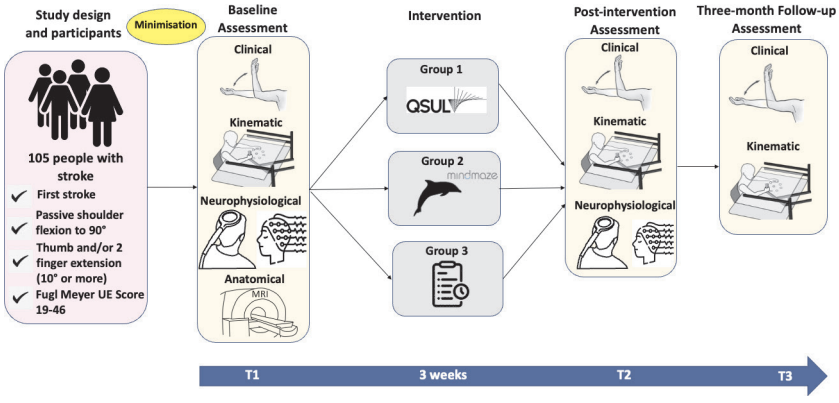

Figure 1 Study timeline from participant recruitment fitting the criteria, three assessment sessions at baseline (T1), post intervention (T2) and 3-month follow-up (T3) and intervention consisting of three groups: (1) Queen Square upper-limb (QSUL) programme, (2) virtual reality-based treatment and (3) waitlist control.

Intervention Description and Replication (TIDIER)[23] for the QSUL programme in online supplemental appendix B). Participants will take part in the QSUL programme alongside usual non-trial participants. The programme has a 1:1 staff/patient ratio (three physiotherapists, three occupational therapists, three rehabilitation assistants for nine patients at any one time). Participants in this trial will receive two daily sessions each of physiotherapy and occupational therapy, supplemented with tailored, individualised interventions delivered by rehabilitation assistants either singly or in groups. Overall, in QSUL, the treatment principle will be based on reducing impairment and promoting re-education of motor control within activities of daily living. Individualised meaningful tasks will be practised repeatedly to facilitate task mastery with a focus on quality of movement. Continuing patient education will be used throughout to embed new skills and knowledge into individual daily routines.

VR-based treatment

Participants have a 90-hour timetable over 3 weeks, aiming to achieve a minimum of 45 hours of time on task (refer to the TIDIER for the VR-based treatment programme in online supplemental appendix C). The VR-based devices and environments will be tailored for each participant, offering two modes: one for reducing arm impairment and restoring control, and the other for restoring finger and hand movement. Participants will spend half of their time on the arm and half of their time on the hand movements.

1. *Arm therapy:* Participants will use the MindPod Dolphin exergame (Mindmaze, Lausanne). The MindPod Dolphin is a CE-marked novel neuroanimation therapy which employs a semi-immersive VR software alongside weight release to encourage high-dose high-intensity exploratory arm movements, focusing on movement quality in a rewarding game-based environment (figure 2). Participants will control a virtual dolphin using their paretic upper limb through a markerless motion capture system (Microsoft 3D Kinect) (figure 2). A passive mechanical exoskeleton for upper-limb gravity compensation, such as the EKSO-UE (Ekso BIONICS, San Rafael, USA) or ShivaExo (ErgoSanté, Anduze, France) equipped with 3D-printed forearm and wrist supports, will be used in this trial. The exoskeleton will be adjusted to match each participant's body weight and muscular strength, facilitating exploratory movement control despite significant motor weakness (figure 2). Three game variations specifically are designed to build to encourage movement in an enriched environment and challenge flexor or extensor synergies that worsen upper-limb impairment.[24]
2. *Hand therapy:* For hand control deficits, force sensors either in the form of a rubber-egg-shaped device (Izar device) or force sensors surrounding each finger individually (Hummingbird device) will be used with the KATA engine, Collibrix and Mind-motion-go software (Mindmaze, Lausanne) (figure 2). Participants will generate either isometric mass finger flexion/extension or individualised isometric finger movements to interact with the diverse games and drive the different virtual creatures to walk through various terrains, progressing from simple to difficult games.

Figure 2 Upper-limb training together with the virtual reality-based treatment setup.

Therapists will monitor participants' training, controlling game progression and adapting arm weight support to maximise the time on task and movement demands. If the participant completes the task successfully, advancement to the next level will be automatic or manually by the physiotherapist depending on the level of frustration, fatigue or signs of demotivation experienced by the participant. Reversion to a previous level may occur if compensatory strategies reappear.

Waitlist control group

Participants will receive their usual care during the 3-week 'treatment' period. In some cases, participants may not be receiving any treatment, but could include community/outpatient therapy, or their own home or gym-based exercise programmes. We will ask participants to record the number of hours of upper-limb activity that they will undertake while on the waitlist.

Outcome measures

All participants will be assessed by trained physiotherapists and occupational therapists on day 1 of treatment (T1), last day (day 15) of treatment (T2) and 3 months after treatment has finished (T3). For all three timepoints, clinical and kinematic measures will be conducted. Neurophysiological measures will be assessed at T1 and T2, and structural MRI scans will be performed at any point during the trial.

Clinical measures

The primary outcome measure will be the FMUE, one of the outcome measures of motor impairment recommended by the SRRR.[25] Secondary outcome measures will be the Action Research Arm Test,[26] Chedoke Arm and Hand Activity Inventory (CAHAI-13),[27] muscle strength (power and pincer grips), elbow flexion (biceps), elbow extension (triceps) using dynamometry, Fugl-Meyer sensory evaluation,[28] Montreal Cognitive Assessment,[29] Stroke Impact Scale 3.0,[30] The Stroke Self-Efficacy Questionnaire[31] and quality of life (EQ-5DL).[32] FMUE, ARAT and CAHAI-13 will be video-recorded and then scored by blinded trained physiotherapists and occupational therapists.

Kinematic

Recent SRRR guidelines encourage the assessment of motor training effects on motor control as assessed with movement kinematics.[10] Kinematics provide valuable insights into spatial and temporal movement quality, distinguishing between behavioural restitution and compensation. In this study, kinematic parameters of the (1) proximal upper limb (shoulder and elbow) and (2) distal upper limb (fingers) will be collected.

1. *Proximal motor control:* Examination of key kinematic parameters will be assessed using the KINARM Exoskeleton (BKIN Technologies Ltd.), a platform to permit movements of both arms in the horizontal plane involving abduction/adduction and flexion/extension movements at the shoulder and elbow joints (figure 3). KINARM Standard Tests (figure 3, left) will provide sensitive and objective measures of integrated sensory, motor and cognitive brain functions through the precise measurement of human behaviour. KINARM Standard Tests will provide a 'task score' for each task at each timepoint for each participant.[33]
2. *Distal motor control:* The ability to move fingers independently will be assessed using a customised task and an ergonomic device (Hummingbird, Mindmaze) that will independently measure finger strength and dexterity from all digits, in both flexion and extension movements. The device will obtain maximum voluntary force for each finger, and finger individuation, by measuring how much the non-instructed fingers participate when only one instructed finger needs to be moved independently.[24 34]

Explanatory variables

The SRRR has recommended incorporating explanatory variables of upper-limb motor impairment, including neurophysiological and neuroimaging metrics.[9]

Corticospinal tract integrity: TMS

Corticospinal tract integrity is an important prognostic factor for upper-limb motor recovery[35] and response to neurorehabilitation interventions[36] and has been recommended by the SRRR as the only 'biomarker' ready to be included in all neurorehabilitation clinical trials.[9] In our study, single-pulse TMS will be used to determine the presence of MEPs in wrist and hand muscles of the upper limb. The participant will be considered 'MEP+' if amplitude of MEPs is observed at a consistent latency (±3 ms) on 50% of at least 10 trials in either of the extensor carpi radialis and/or first dorsal interosseous.[37] Recruitment curves will also be recorded and analysed in those who are 'MEP+' from the ipsilesional motor cortex of each participant as alternative metrics for secondary analysis.[35] The RC will be constructed for each participant, at each muscle, using the averaged peak-to-peak MEP amplitude value, plotted against each corresponding increment of TMS stimulus intensities (90–140% of RMT). Curve fitting was done using MATLAB to fit a sigmoidal curve to the data. Two main parameters will be computed: the coefficient of determination (R^2) and the area under the curve (AUC). R^2 will be obtained from the goodness-of-fit assessment using the curve-fitting function in MATLAB. After the accuracy fit will be determined, the AUC per muscle will be calculated (AUC_{FDI} and AUC_{ECR}).

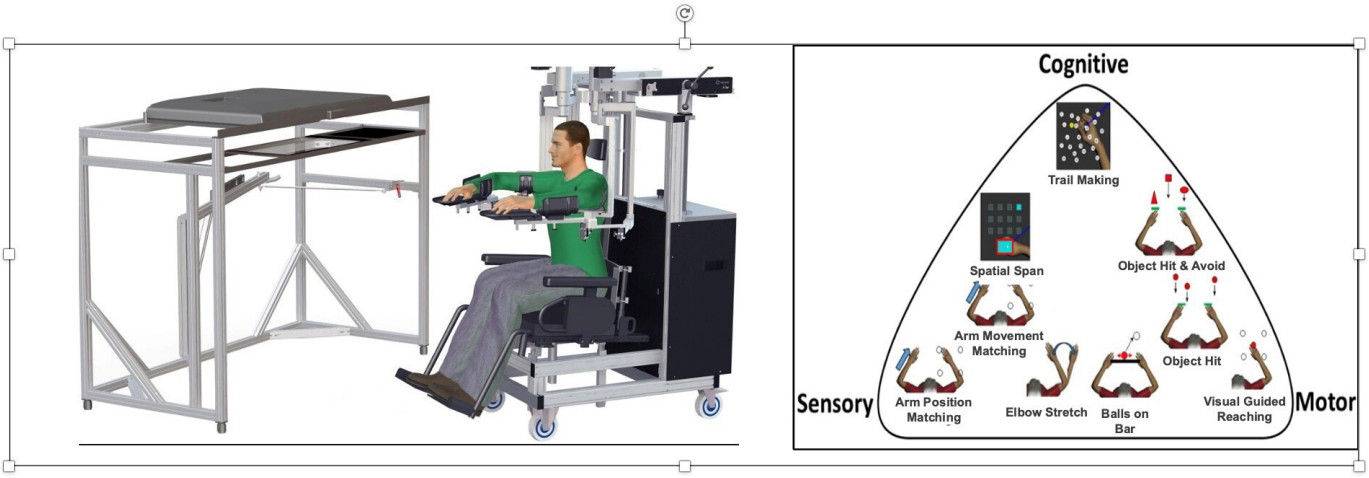

Figure 3 Left: KINARM exoskeleton. Right: KINARM Motor, Sensory and Cognitive tasks.

Dorsal column-medial lemniscal pathway integrity: EEG

The presence or absence of median nerve SEP measured with EEG may also provide valuable information on responders to high-dose upper-limb rehabilitation. The absence of SEPs indicates poor outcome at 2 months post stroke, and combining clinical motor scores with SEPs improved arm recovery prediction.[38] In our study, we will record SEPs using a 64-channel EEG system with scalp electrodes placed according to the 10–20 system.[39] Median nerve stimulation will be administered at seven intensities, ranging from sensory to motor thresholds (100–150% of motor threshold).[40] Surface electromyography will be recorded from the abductor pollicis brevis muscle using surface electrodes with data digitised at 4 kHz for offline analysis. EEG data will be processed offline in MATLAB (MathWorks, USA). Using EEGLab, data will be filtered using a high-pass Butterworth filter to remove slow drifts and trials contaminated by artefacts will be corrected with an independent component analysis (ICA) algorithm. To analyse SEP data, an average trace for each stimulation intensity will be produced to extract the N20 latency and N20/P25 amplitude.

Resting-state functional connectivity: EEG

The level of functional connectivity could be also a predictor of treatment gains from neurorehabilitation.[41] In our study, participants will also undergo resting-state EEG data collection for up to 8 min with their eyes open. Rest EEG data were filtered with a high-pass (windowed sinc FIR filter, cut-off frequency 0.1 Hz, filter order 826) and low-pass filtered (windowed sinc FIR filter, cut-off frequency 35 Hz, filter order 166), downsampled to 250 Hz. Bad channels will be interpolated (spherical spline interpolation), stereotypical artefacts attenuated also using ICA and non-stereotypical artefacts will be removed using Artifact Subspace Reconstruction. A first-level analysis model of the data within each individual participant's EEG data will then be conducted. Power spectral density will be computed for each data set and channel using a 2 s segment length, a 1 s overlap between segments and a Hamming taper. The first-level analysis will be extended to group analyses by carrying a set of first-level results to a second-level general linear model (GLM). This group-level analysis models between-subject variability across independent first-level GLM-Spectra.[42]

Lesion load and grey and white matter integrity: MRI

Using whole-brain topographic information about stroke damage could also enhance treatment response predictions.[11] In our study, we will perform structural 3.0T MRI (scanner type) on all MRI-compatible subjects. All MRI scans will be acquired at the Wellcome Centre for Human Neuroimaging or at the National Hospital for Neurology and Neurosurgery. Stroke lesions will be demarcated using the semiautomated segmentation algorithm (https://www.medizin.uni-tuebingen.de/de/das-klinikum/einrichtungen/kliniken/kinderklinik/kinderheilkunde-iii/forschung-iii/software) applied to the axial T1-w MRIs. Lesion maps will be smoothed using a 2 mm full-width half-maximum Gaussian kernel. Lesions will be normalised to standard MNI space and left hemispheric lesions will be flipped. To characterise structural connections, we will quantify voxel-wise per cent disconnection maps and the effect of the lesion on the relevant association, projection and commissural connections, again using the Lesion Quantification Toolkit.[43]

Statistical analyses

All data will be accessed by the trial team. We will use Fisher's exact test or the χ^2 test to assess differences in baseline values for nominal data, the Mann-Whitney U test for ordinal data and Student's t-test for independent groups for other outcomes. Analysis of the primary and secondary outcomes will follow the intention-to-treat principle. For the primary analysis, regression analysis will evaluate the differences in the overall effect of QSUL or VR-based treatment and waitlist groups at T3 on FMA-UE. For secondary analysis, regression analysis will also evaluate the differences in the overall effect of QSUL or VR-based treatment and waitlist groups at T2 and T3 on FMA-UE, secondary clinical outcome measures, kinematic and neurophysiological measures (MEP and SEP amplitudes, functional connectivity). Also, as part of secondary analysis, a multiple regression model will be used to study the level of recovery on the FMA-UE, based on multiple explanatory variables including secondary clinical and kinematic measures, and neurophysiological parameters; presence or absence of MEP and SEP, resting-state EEG frequency domains, lesion load and white/grey matter integrity. The participant ID will be used as a random intercept to account for individual differences in baseline demographic characteristics.

Recording of adverse events

All adverse events will be recorded in the medical records in the first instance, in the Case Report Form following consent and with clinical symptoms and accompanied with a simple, brief description of the event, including dates as appropriate.

Ethics and dissemination

The study has been approved by the Wales Research Ethics Committee 2 Cardiff (Rec reference: 22/WA/0065). Trial results will be disseminated through peer-reviewed publications, presentations at major stroke/neurorehabilitation conferences and outreach to relevant stakeholder communities.

DISCUSSION AND SUMMARY

The INTENSIVE trial will provide information on the efficacy of high-dose high-intensity upper-limb neurorehabilitation for patients with chronic strokecompared with their current usual care. The findings will inform evidence-based clinical practice guideline recommendations allowing for clearer health policy. The trial is

principally designed to compare high-dose high-intensity neurorehabilitation to low-dose usual care, rather than to directly compare different ways of delivering high-dose high-intensity neurorehabilitation. However, we expect to be able to generate further data-led hypotheses about the differential effects of conventional treatment compared with VR-based treatment (at the same dose) on a range of secondary measures assessing both motor impairment and disorders of activity, as well as across other domains, including sensation, cognition, quality of life and patients' own perceptions about the impact of stroke on their lives. Furthermore, we will be able to generate data-led hypotheses about whether treatment effects are maintained better with conventional compared with VR-based treatment.

Following the recommendations of the SRRR consensus documents[9 10] we have also included (1) kinematic measures as secondary outcome measures in order to assess the effect of treatment on motor control and (2) explanatory measures of structural and functional damage to the brain, in particular ascending and descending white matter pathways, in order to look for characteristics that might have an effect on treatment response.

X Lisa Tedesco Triccas @ltriccas

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Consent obtained directly from patient(s).

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ORCID iD

Lisa Tedesco Triccas http://orcid.org/0000-0001-9097-9352

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