Robot Assisted Training for the Upper Limb after Stroke

RATULS

Study Protocol

Version 4: 30 June 2017

Study Funder:
Health Technology Assessment Programme
National Institute for Health Research
Evaluation, Trials and Studies Coordinating Centre
University of Southampton
Alpha House
Enterprise Road
Southampton
SO16 7NS

Study Sponsor:
Newcastle upon Tyne Hospitals NHS Foundation Trust
Joint Research Office
6th Floor, Leazes Wing
Royal Victoria Infirmary
Queen Victoria Road
Newcastle upon Tyne
NE1 4LP

Chief Investigator:
Professor Helen Rodgers
Professor of Stroke Care
Stroke Research Group
Institute of Neuroscience
Newcastle University
3-4 Claremont Terrace
Newcastle upon Tyne
NE2 4AE

Contents

Protocol contacts

Chief Investigator:

Name:	Professor Helen Rodgers
	Professor of Stroke Care
Address:	Stroke Research Group
	Newcastle University
	3 – 4 Claremont Terrace
	Newcastle upon Tyne
	NE2 4AE
Phone:	0191 208 8025
Fax:	0191 208 5540
Email:	helen.rodgers@ncl.ac.uk

Project Manager:

Name:	Dr Lisa Shaw
	Senior Research Associate
Address:	Stroke Research Group
	Newcastle University
	3 – 4 Claremont Terrace
	Newcastle upon Tyne
	NE2 4AE
Phone:	0191 208 3826
Fax:	0191 208 5540
Email:	lisa.shaw@ncl.ac.uk

Contact for study sponsor:

Name:	Ms Amanda Tortice
	Head of Joint Research Office
Address:	Joint Research Office
	6th Floor, Leazes Wing
	Royal Victoria Infirmary
	Queen Victoria Road
	Newcastle upon Tyne
	NE1 4LP
Phone:	0191 282 5213
Fax:	0191 208 5164
Email:	amanda.tortice@ncl.ac.uk

Grant award holders

Chief investigator:

Professor Helen Rodgers, Professor of Stroke Care, Institute of Neuroscience, Newcastle University, 3-4 Claremont Terrace, Newcastle upon Tyne, NE2 4AE. Email: helen.rodgers@ncl.ac.uk

Co-investigators:

Mrs Lydia Aird, Specialist Physiotherapist in Stroke, Northumbria Healthcare NHS Foundation Trust, North Tyneside General Hospital, Rake Lane, North Shields, NE29 8NH. Email: lydia.aird@northumbria-healthcare.nhs.uk

Dr Sreeman Andole, Clinical and Research Lead in Stroke, Barking, Havering & Redbridge University Hospitals NHS Trust, Queen's Hospital, Rom Valley Way, Romford, Essex, RM7 0AG. Email: sreeman.andole@bhrhospitals.nhs.uk

Dr David Cohen, Consultant Physician, General & Geriatric Medicine, North West London Hospitals NHS Trust, Northwick Park Hospital, Watford Road, Harrow, HA1 3UJ. Email: david.cohen@nhs.net

Dr Jesse Dawson, Clinical Senior Lecturer in Medicine, University of Glasgow, Queen Elizabeth University Hospital, 1342 Govan Road, Govan, Glasgow, G51 4TF. Email: jesse.dawson@glasgow.ac.uk

Professor Janet Eyre, Professor of Paediatric Neuroscience, Newcastle University, Department of Child Health, Royal Victoria Infirmary, Queen Victoria Road, Newcastle upon Tyne, NE1 4LP. Email: janet.eyre@ncl.ac.uk

Dr Tracy Finch, Senior Lecturer in Psychology of Health Care, Newcastle University, Institute of Health & Society, Baddiley-Clark Building, Richardson Road, Newcastle upon Tyne, NE2 4AX. Email: tracy.finch@ncl.ac.uk

Professor Gary Ford, Chief Executive Officer, Medical Sciences Division, University of Oxford, and Oxford University Hospitals NHS Foundation Trust. Oxford Academic Health Science Network, Magdalen Centre North, John Eccles House, Robert Robinson Avenue, Oxford Science Business Park OX4 4GAP. Email: gary.ford@ouh.nhs.uk

Mr Steven Hogg, Lay Member, North East Stroke Research Network, Education Centre, Sunderland Royal Hospital, Sunderland, SR4 7TP.

Ms Denise Howel, Senior Lecturer in Statistics, Newcastle University, Institute of Health and Society, Baddiley-Clark Building, Richardson Road, Newcastle upon Tyne, NE2 4AX. Email: denise.howel@ncl.ac.uk

Dr Niall Hughes, Consultant Physician, Queen Elizabeth University Hospital, 1342 Govan Road, Govan, Glasgow, G51 4TF. Email: Niall.Hughes@ggc.scot.nhs.uk

Dr Hermano Igo Krebs, Principal Research Scientist & Lecturer, Massachusetts Institute of Technology, 77 Massachusetts Avenue, 3-137 Cambridge, MA 02139, USA. Email: hikrebs@mit.edu

Dr Christopher Price, Clinical Senior Lecturer in Medicine, Northumbria Healthcare NHS Foundation Trust, Wansbeck General Hospital, Woodhorn Lane, Ashington, Northumberland NE63 9JJ. Email: christopher.price@northumbria-healthcare.nhs.uk

Professor Lynn Rochester, Professor Human Movement Science, Newcastle University, Institute for Ageing & Health, Clinical Ageing Research Unit, Campus for Ageing & Vitality, Newcastle upon Tyne, NE4 5PL. Email: lynn.rochester@ncl.ac.uk

Dr Lisa Shaw, Senior Research Associate, Newcastle University, Institute of Neuroscience, 3-4 Claremont Terrace, Newcastle upon Tyne, NE2 4AE. Email: lisa.shaw@ncl.ac.uk

Dr Laura Ternent, Lecturer in Health Economics, Newcastle University, Institute of Health & Society, Baddiley-Clark Building, Richardson Road, Newcastle upon Tyne, NE2 4AX. Email: laura.ternent@ncl.ac.uk

Professor Duncan Turner, Professor of Restorative Neuroscience & Rehabilitation, University of East London, School of Health, Sport and Biosciences, Stratford Campus, Water Lane, Stratford, London, E15 4LZ. Email: d.l.turner@uel.ac.uk

Professor Luke Vale, Health Foundation Chair in Health Economics, Newcastle University, Institute of Health & Society, Baddiley-Clark Building, Richardson Road, Newcastle upon Tyne, NE2 4AX. Email: luke.vale@ncl.ac.uk

Professor Frederike van Wijck, Reader in Neurological Rehabilitation, Institute for Applied Health Research and School of Health and Life Sciences, Glasgow Caledonian University, Cowcaddens Road, Glasgow, G0 4BA. Email: FrederikevanWijck@gcu.ac.uk

Professor Scott Wilkes, Professor of General Practice and Primary care, Department of Pharmacy, Health and Wellbeing, Faculty of Applied Sciences, Science Complex, City Campus, Chester Road, University of Sunderland, SR1 3SD. Email: scott.wilkes@sunderland.ac.uk

Protocol signature page

Local site principal investigator signature:

I have read and agree to version 4 of the protocol dated 30 June 2017 entitled "**Robot Assisted Training for the Upper Limb after Stroke (RATULS)**".

I am aware of my responsibilities as an Investigator under the Research Governance Framework for Health and Social Care. I agree to conduct the study according to these guidelines and to appropriately direct and assist the staff who will be involved in the study locally.

Name……Signature …… Date ……

Affiliation……..

Glossary

Abbreviation	Definition
AE	Adverse Event
ADL	Activities of Daily Living
AR	Adverse Reaction
CEA	Cost-effectiveness analysis
LCRN	Local Clinical Research Network
CTO	Clinical Trial Officer
CTU	Clinical Trial Unit
DMEC	Data Monitoring and Ethics Committee
HTA	Health Technology Assessment
ICER	Incremental cost effectiveness ratio
MOCA	Montreal Cognitive Assessment
MIT	Massachusetts Institute of Technology
NIHR	National Institute for Health Research
NIHSS	National Institute of Health Stroke Scale
NHS	National Health Service
NRES	National Research Ethics Service
PI	Principal Investigator
PIS	Patient Information Sheet
QALY	Quality Adjusted Life Years
RATULS	Robot Assisted Training for the Upper Limb after Stroke
RCT	Randomised Controlled Trial
R+D	Research and Development
REC	Research Ethics Committee
SAE	Serious Adverse Event
SIS	Stroke Impact Scale
SRN	Stroke Research Network
TMG	Trial Management Group
TSC	Trial Steering Committee
VISTA	Virtual International Stroke Trials Archive

Protocol summary

Title: Robot Assisted Training for the Upper Limb after Stroke (RATULS).

Chief Investigator: Professor Helen Rodgers.

Sponsor: Newcastle upon Tyne Hospitals NHS Foundation Trust.

Funder: NIHR HTA programme (ref: 11/26/05).

Study design: A pragmatic multicentre randomised controlled trial; cost analysis and process evaluation.

Study setting: NHS stroke services. There are four study centres, each consisting of a hub site with an InMotion robotic gym system and adjacent stroke services which will be spoke sites.

Study participants: Adults with acute or chronic stroke causing moderate to severe upper limb functional limitation.

Study treatments: There are three randomisation groups:
i. Robot assisted training using the InMotion robotic gym system
ii. Enhanced upper limb therapy
iii. Usual care

Randomisation: Individual participant randomisation stratified by centre, time since stroke, and severity of upper limb impairment via an independent randomisation service.

Primary outcome: Upper limb function measured by the Action Research Arm Test (ARAT) at three months post randomisation.

Secondary outcomes: Upper limb impairment, activities of daily living, quality of life, resource use and adverse events measured at three and six months post randomisation.

Blinding: Outcomes assessments will be undertaken by a blinded assessor.

Parallel qualitative process evaluation: Semi-structured interviews with participants and health service professionals to seek their views and experiences of the upper limb rehabilitation they have received or provided, and factors affecting the implementation of the trial.

Sample size: Allowing for 15% attrition, 762 participants are needed to provide 80% power (significance level 1.67 % because of multiple comparisons) to detect a 15% difference in 'successful outcome' between each of the three pairs of treatments (robot assisted training, enhanced upper limb therapy, usual care). Successful outcome is defined as: baseline ARAT 0-7 must improve by three or more points; baseline ARAT 8-13 must improve by four or more points; baseline ARAT 14-19 must improve by five or more points; baseline ARAT 20-39 must improve by six or more points.

Study duration: 68 months.

Background

Loss of arm function is a common and distressing consequence of stroke. Currently it is unclear how best to provide therapy to improve arm recovery. A 2009 systematic review reported that improvements in recovery of arm function have been observed in trials evaluating constraint-induced movement therapy, EMG biofeedback, mental practice with motor imagery, and robotics[1]. The review concluded that 'trials of robotics have relatively large effect sizes but are limited by the small number of participants…the results could easily be overturned by new trials'.

Neuroscientists and clinicians have moved away from the static perception that the brain is hardwired to a new dynamic understanding that plasticity occurs and might be harnessed to remap or create new neural pathways[2]. The working model behind therapy aimed at reducing impairment and not substitution is best expressed by Hebbian ideas of nervous system plasticity, mainly that neurons which "fire" together, "wire" together[3]. The human brain is capable of self-organization, or neuroplasticity, so that training and rehabilitation offer an opportunity for motor recovery. The scientific rationale for using robot assisted training in upper limb rehabilitation is anchored on this concept of motor plasticity and on evidence that intensive repetition of movement promotes motor recovery following a stroke[4, 5].

Robot assisted training is increasingly becoming part of post-stroke rehabilitation in many countries. Rehabilitation robots can perform repetitive tasks in a highly consistent and controllable manner, and they can continuously record patients' movement kinematics and dynamic features. Such features can be used to not only quantify therapy outcomes, but also to design a robot control loop which tailors the therapeutic action of the robot to the patient's motor abilities. Since the publication of the first controlled study with stroke inpatients in 1997[6] several studies have been completed with both stroke inpatients and outpatients demonstrating the potential of robotic assisted training for upper limb rehabilitation and recovery[7-10].

This study will evaluate the InMotion robotic gym system which was specifically designed for clinical rehabilitation applications. This is currently the best available technology for robot assisted training for patients with moderate to severe upper limb impairment post stroke. It has CE medical approval and is supported by an infrastructure for production, distribution and maintenance. The InMotion robotic gym system consists of three robot modules to train the upper limb: shoulder-elbow module, wrist module, hand module. The patient sits at a table and places their affected arm onto the InMotion arm support and attempts to move their arm/hand/wrist to play games on the InMotion computer screen. Movements are assisted by InMotion if the patient cannot perform the movements themselves. The InMotion robotic gym system is shown in Figure 1 and the following link shows it being used in clinical settings. http://interactive-motion.com/news.htm

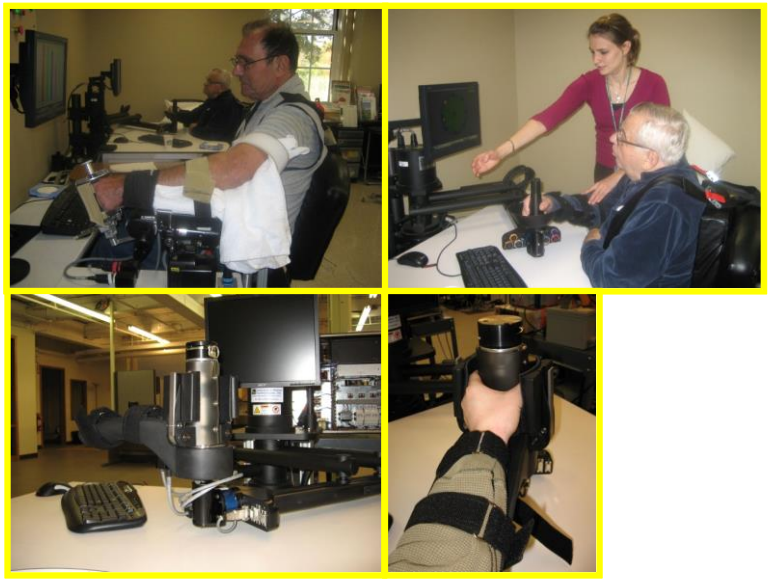


Figure 1: InMotion robotic gym system. Top row left panel shows the wrist robot and the right panel the shoulder-and-elbow module. Bottom row shows the hand module, which assists digit extension /flexion mounted at the tip of the shoulder-and-elbow robot.

The InMotion robotic gym system is configured for safe, stable and compliant operation in close physical contact with patients. This is achieved using impedance control, a key feature of the robot control system[11]. Its computer control system modulates the way the robot reacts to mechanical perturbation from a patient or clinician and ensures a gentle compliant behaviour - technically, a low and controllable impedance. Operationally, a low impedance means that the robot can "get out of the way" as needed. It can therefore be programmed to provide assist-as-needed and allow the stroke patient to express movement, in whole or in part, even when the attempts are weak or poorly coordinated[12]. The InMotion robotic gym system is in the unique position to offer modularity of configuration. Significant advantages of modularity include the ability to tailor device configurations to specific impairments and efficient resource utilization as the modules within the InMotion robotic gym system may be de-coupled for standalone use allowing two patients to be treated simultaneously.

The system development started in 1989 and it has amassed by far the largest body of clinical evidence of any other robotic system[8, 13, 14]. It has been successfully tested in clinical studies involving over 800 stroke patients and there are around 250 robots in use worldwide. A key study was published in the New England Journal of Medicine in 2010[8]. This study recruited 127 patients with moderate to severe upper limb impairment six months or more after stroke from four centres in the USA. Participants were randomised to receive robot assisted therapy (n=49); intensive comparison therapy (n=50); or usual care (n=28). Therapy consisted of 36 one hour sessions over 12 weeks. The study found that robot assisted therapy did not improve upper limb motor function at 12 weeks compared with intensive therapy or usual care (the primary outcome). However, participants who received robot assisted training had significantly better results at 12 weeks on the Stroke Impact Scale than those who received usual care. In secondary analyses, improvements were seen in motor function of those who received robot assisted training compared with usual care but not intensive therapy at 36 weeks. The added costs of delivering robot or intensive comparison therapy were recuperated by lower healthcare costs compared to those with usual care[15].

A 2012 Cochrane systematic review of electromechanical and robot assisted arm training after stroke reported outcomes from 666 patients who participated in 19 trials (four trials evaluated the InMotion robotic gym system). Improvements in arm function and activities of daily living were reported, but that the results should be interpreted with caution due to differences between the trials[9].

Study aim and objectives

Aim

To determine whether robot assisted training with the InMotion robotic gym system (In Motion commercial version) improves upper limb function post stroke.

Objectives

- To determine whether robot assisted training (group 1) improves upper limb function post stroke compared to an enhanced upper limb therapy programme (group 2) or usual care (group 3).

- To determine whether robot assisted training (group 1) improves upper limb impairment, activities of daily living and quality of life compared to an enhanced upper limb therapy programme (group 2) or usual care (group 3).

- To model the costs of robotic assisted training compared to an enhanced upper limb therapy programme or usual care.

- To seek the views and experiences of patients and health service professionals about the upper limb rehabilitation they have received or provided and factors affecting the implementation of the trial.

- To explore:
  - the time pattern of upper limb recovery of participants in each treatment group.
  - the impact of the severity of baseline upper limb function and time since stroke upon the effectiveness of the interventions.

Outcome measures

The primary outcome is upper limb function measured by the Action Research Arm Test[16] (ARAT) at 3 months. Secondary outcomes are upper limb impairment (Fugl-Meyer Test[17]), activities of daily living (Barthel ADL Index[18, 19]), quality of life (Stroke Impact Scale[20], EQ-5D-5L[21]) and adverse events including upper limb pain (numerical rating scale[22]) measured at 3 and 6 months.

Study design

This project will use a multi-method approach to evaluate robot assisted training for the upper limb post stroke. A three arm multicentre randomised controlled trial (RCT), cost analysis and process evaluation including a qualitative description of the experience of patients and health service professionals will be conducted. Group 1 will receive robot assisted training using the InMotion robotic gym system. Group 2 will received an enhanced upper limb therapy programme based upon current evidence based practice and national guidelines. Group 3 will receive usual post stroke care. The RCT will commence as an internal pilot and continue to the full study if the progression criteria are achieved.

Study setting

The study will take place in stroke services in the UK. There will be four RATULS study centres (Glasgow, North Tyneside, Northwick Park and Romford) consisting of a hub site with an InMotion robotic gym system and stroke services in adjacent Trusts which will be spoke sites. Study participants will be recruited from the population served by each study centre and identified from a number of sources including stroke units, outpatient clinics, day hospitals, community rehabilitation services, local stroke clubs and primary care databases. The InMotion robotic gym system is not portable so participants who are randomised to receive robot assisted training will travel to a hub stroke unit to receive this treatment. Participants randomised to receive enhanced upper limb therapy may be treated by their local stroke service or the hub stroke service according to local preference and travelling distances. Participants randomised to usual care will be treated by their local stroke service.

Study participants

Adults with a first ever stroke who fulfil the following criteria are eligible:

Inclusion criteria

- Age 18 years and over
- Clinical diagnosis of stroke (cerebral infarction, primary intracerebral haemorrhage, subarachnoid haemorrhage)
- Between one week and five years since stroke
- Moderate to severe upper limb functional limitation (ARAT[16] score 0-39) due to stroke.
- Able to provide consent to take part in the study and to comply with the requirements of the protocol

Exclusion criteria

- More than one stroke (patients with previous TIA may be invited to participate)
- Other current significant impairment of the upper limb affected by stroke e.g. fixed contracture, frozen shoulder, severe arthritis, recent fracture
- Diagnosis likely to interfere with rehabilitation or outcome assessments e.g. registered blind
- Previous use of the InMotion robotic gym system or other arm rehabilitation robot
- Current participation in a rehabilitation trial evaluating upper limb rehabilitation after stroke
- Previous enrolment in this study

Case ascertainment, recruitment and consent

Study participants will be recruited from both incident and prevalent stroke populations. Participants will be sought from a number of settings in primary and secondary care including stroke units, outpatient clinics, day hospitals, community rehabilitation services and general practices. A recruitment strategy will be developed for each study centre with the aim of including similar numbers of participants within 0-3 months of stroke (1/3), >3 -12 months after stroke (1/3) and >12 months to five years after stroke (1/3).

Potential participants from secondary care

Potentially eligible participants treated by secondary care services will be identified by local clinicians and/or staff from the Local Clinical Research Network (LCRN) who are supporting stroke studies at each participating site. LCRN staff are part of the hospital stroke team and they liaise regularly with clinical teams to identify which patients may be invited to participate in stroke research studies. Some patients with acute stroke may not be able to initially comply with the protocol but will be invited to participate if they improve subsequently. LCRN staff will approach potentially eligible patients, discuss the study and provide a study information leaflet. After allowing sufficient time for the information to be considered, the LCRN staff will ascertain whether the patient is potentially interested in taking part in the study. Written informed consent

will be subsequently obtained. According to local preference, this may be obtained by the LCRN staff, or, by the local study co-ordinator (senior healthcare professional) based at each study hub. The local study co-ordinator and/or LCRN staff will also perform screening and baseline assessments which follow consent (as below). The logistics of performing these procedures will be determined locally.

Potential participants may also be identified from hospital stroke discharge summaries/clinic letters. If this method is used, LCRN staff will screen discharge summaries and clinic letters, and potential participants will be approached by letter from the local principal investigator. Enclosed with the letter will be a short RATULS leaflet, a patient information sheet, a RATULS reply slip and a pre-paid envelope. As discharge summaries/clinic letters may not provide information about current upper limb deficits, the invitation letter will detail the main study eligibility criteria and ask interested patients to contact their local LCRN staff or study co-ordinator (according to local preference) for further information. Interested patients may make contact by telephone or by return of the RATULS reply slip (which will give their telephone number for the LCRN staff/study co-ordinator to call back).

On the telephone, the local LCRN staff/study co-ordinator will ask a few short questions to confirm potential study eligibility (eg check that the interested patient has moderate to severe upper limb functional limitation) and if appropriate, arrange an appointment for further discussion. At the appointment, further details about the study will be provided. Informed consent will subsequently be obtained if the patient wishes to take part.

According to local preference, invited patients who have not telephoned the LCRN staff/study co-ordinator or returned the reply slip within four weeks may receive either a follow up invitation letter or a follow up telephone call from the LCRN staff/study co-ordinator.

Each participating secondary care site will keep a record of all patients invited by letter, and a screening log for all inpatients/outpatients considered for the study and subsequently included or excluded.

Potential participants from primary care

To identify and recruit participants from primary care, a local primary care recruitment strategy will be prepared with support from LCRN staff supporting primary care studies in the four geographical study areas. This strategy will detail the number of local GP research practices who will be asked to identify participants to be invited to take part in the study, the number of potential participants for each practice to invite, and a time line for the invitations to be issued.

With support from LCRN staff, each invited practice will perform a database search using the study inclusion/exclusion criteria. As the primary care databases are unlikely to be sufficiently detailed for the search to list only patients meeting the complete study eligibility criteria, the searches are likely to identify more patients than will be study eligible and can be invited. From the database list, each practice will subsequently select patients to be invited to take part in the study. The selection process may vary according to local preference, but is likely to be of the form of choosing every n/x patient where n is number of patients identified in the database search and x is the number of patients for the practice to invite. To meet the requirements of the study, selection may also be based on time from stroke and advice from local GPs about appropriateness of approaching individuals to take part in the study.

Each selected patient will be sent an invitation letter with enclosed short RATULS leaflet, patient information sheet, RATULS reply slip and pre-paid envelope, by their GP. The invitation letter will detail the main study eligibility criteria and ask interested patients to contact the LCRN staff or study co-ordinator for further information (according to local preference). Interested patients may make contact by telephone or by return of the RATULS reply slip (which will give their telephone number for the LCRN staff/study co-ordinator to call back).

On the telephone, the LCRN staff/study co-ordinator will ask a few short questions to confirm

potential study eligibility (eg check the interested patient has moderate to severe upper limb functional limitation) and if appropriate, arrange an appointment for further discussion. At the appointment, further details about the study will be provided. Informed consent will subsequently be obtained if the patient wishes to take part.

According to local preference, invited patients who have not telephoned the LCRN staff/study co-ordinator or returned the reply slip within four weeks may receive either a follow up invitation letter or a follow up telephone call from their GP practice.

Each GP practice will keep a record of all invited patients. Hospital based LCRN staff and primary care LCRN staff will work closely to ensure potential participants are not approached on multiple occasions.

Potential patients from other sources

As some individuals may not be in contact with primary or secondary care services, local community stroke clubs and day centres will also be given information about the study. In addition, some individuals may hear about the study from a press release or see information about the study on a poster or RATULS leaflet. Interested individuals will be able to contact the local study co-ordinator/LCRN staff directly for a discussion about the study. If an individual is interested in taking part in the study and potentially eligible, an appointment for further discussion will be made. At the appointment, further details about the study will be provided. Informed consent will subsequently be obtained if the patient wishes to take part.

Consent forms

Original consent forms will be retained in the investigator site file at each study site. A copy of the form will be filed in the hub site file (if different from the site of consent), medical notes and/or in the GP records if identified in primary care. A further copy will be given to the participant. A letter will be sent to the patient's GP to inform them about participation in this study. Consent for this will be sought on the consent form.

The information sheets and consent forms will be available in English. However, interpreters and translation of written material will be possible through local NHS arrangements should potentially eligible patients require this.

Loss of capacity to consent to research during participation in the study

It is possible that the participants in this study may temporarily (e.g. because of intercurrent illness) or permanently (e.g. because of further stroke) lose the capacity to consent to participate in this research project. In either case, it is unlikely that they will be able to continue with study treatments or research outcome assessments. In the event of likely temporary incapacity, study treatments will be stopped whilst the participant is unwell but restarted on recovery if the participant wishes to continue (treatment will end in the original timescale to allow outcome data to be collected at the end of the treatment period, not all lost treatment sessions will be replaced). In the event of permanent incapacity, the participant will be withdrawn from the study. Data collected prior to withdrawal will be retained and used in the study analysis.

Screening assessment

Once informed consent has been obtained, a screening assessment will be performed by the local study centre coordinator or LCRN staff (according to local preference). The following data will be collected: demography; stroke details; comorbidity; and upper limb function (ARAT[16] score). If the patient fulfils the study inclusion and exclusion criteria, the local study coordinator/LCRN staff will proceed to the baseline assessment. If any of the inclusion or exclusion criteria are not fulfilled, the patient will be informed that they will not be able to take part in this study and thanked for their time. Should it not be possible to complete the baseline

assessment on the same day as the screening assessment, eligibility for the study will be re-confirmed on the day of the baseline assessment.

Baseline assessment

The following baseline data will be collected by the local study co-ordinator/LCRN staff: stroke severity (National Institute for Health Stroke Scale[23]); cognitive function (Montreal Cognitive Assessment[24]); language skills (Sheffield Aphasia Screening Test[25]); upper limb impairment (Fugl-Meyer Test[17] (motor and sensory arm sections)); activities of daily living (Barthel ADL Index[18, 19]); quality of life (EQ-5D-5L[21]); upper limb pain (numerical rating scale[22]) and current upper limb rehabilitation treatments.

In addition, patients will be given a self completion questionnaire containing pre-study resource utilisation questions (adaption of the Client Services Receipt Inventory[26-28]) which they will be asked to complete at the end of the face to face assessment.

Randomisation

Randomisation will be by a central independent web based service hosted by Newcastle University Clinical Trials Unit. Participants will be stratified according to study centre, time since stroke and severity of upper limb impairment (ARAT[16] score), and randomised to groups 1-3 using permuted block sequences. The local study coordinator/LCRN staff will perform randomisation following completion of the baseline assessment. At randomisation, each participant will be allocated a unique study number.

Study treatments

Group 1: Robot assisted training using the InMotion robotic gym system

Group 1 will receive robot assisted training using the InMotion robotic gym system provided for up to 45 minutes per day, three days per week for 12 weeks, in addition to usual care. One hour will be allowed for each training session to enable participants to be assisted on and off the robotic equipment.

Three modules of the InMotion robotic gym system will be used for upper limb rehabilitation.

- module A: shoulder-elbow
- module B: wrist
- module C: hand

Training sessions using all robot modules will consist of point-to-point movements to sequentially presented targets.

The shoulder-elbow module:
The centre of the workspace is located in front of an individual at the body midline with the shoulder elevation at 30˚ with the elbow slighted flexed. The point-to-point tasks start at the centre of the workspace and cause movement to extend radially in eight different directions.

The wrist module:
The centre of the workspace is located in front of an individual and either to the right or left depending on the arm to be trained with the shoulder abduction and elevation around 65˚ and 30˚ respectively. The point to point movements include flexion/extension, abduction/adduction and pronation/supination.

The hand module integrated onto the shoulder-elbow module:
Training sessions using the hand module integrated onto the shoulder-elbow module address unilateral functional abilities, such as reach-and-sweep and pick-and-place. During these goal-directed activities, an individual is presented with tasks requiring the practice of whole-arm movements that involve limb transport and grasp/release.

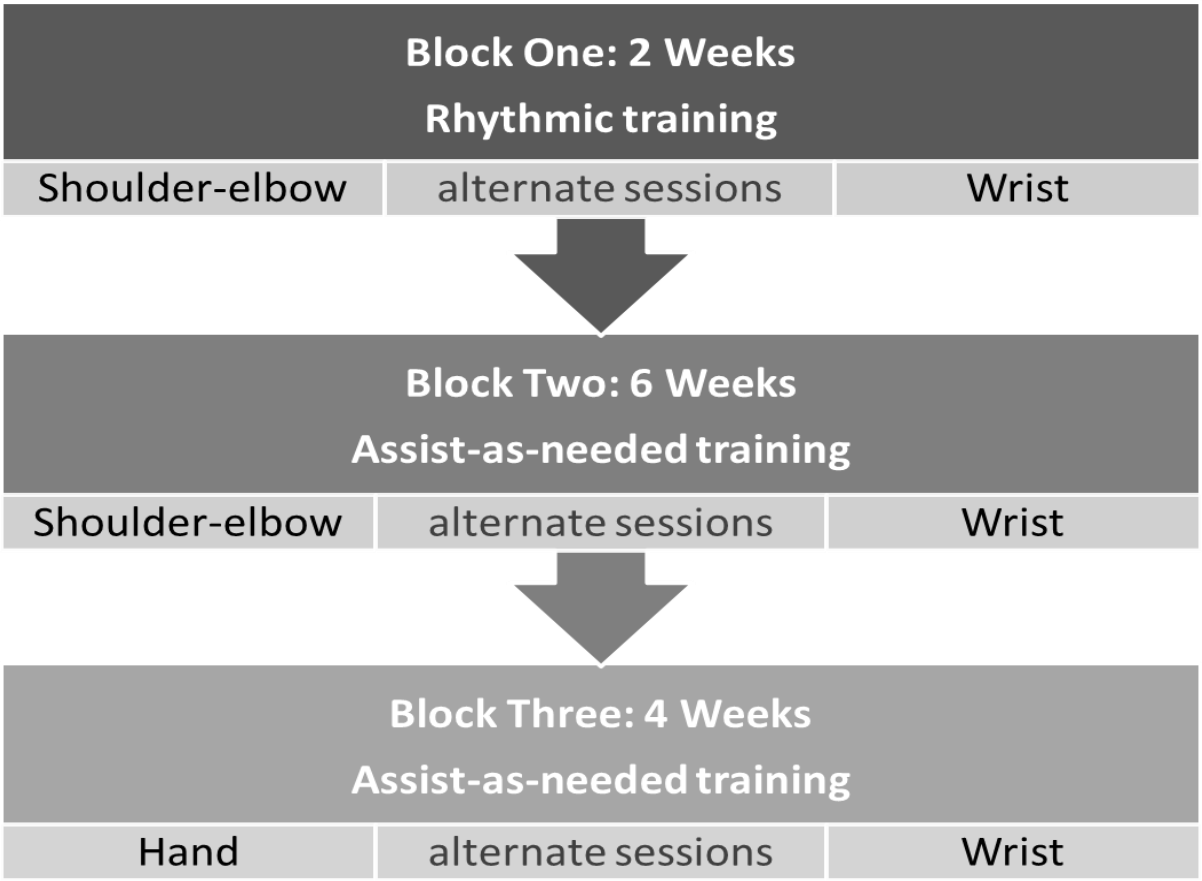
The training programme will be divided into three consecutive blocks in order to integrate training with all three modules. Training sessions on all modules will consist of high repetitions (> 700) of point-to-point movements.

Block one: Block one will last for two weeks and employs alternate training sessions with the shoulder-elbow module A and the wrist module B (three sessions on each module). In block one, the robot modules will rhythmically move the participant to reach the sequentially presented targets.

Block two: Block two will last for six weeks and employs alternate therapy sessions with the shoulder-and-elbow module A and the wrist module B (nine sessions on each module). In block two, the robot modules will allow the participant to attempt to move towards the sequentially presented targets unassisted but will assist if the participant needs help to reach the target.

Block three: Block three will last for four weeks and employs alternative therapy sessions with the hand module C integrated on the shoulder-elbow module A, and the wrist module B (six sessions on each module). As in block two, the robot modules will allow the participant to attempt to move towards the targets unassisted but will assist if the participant needs help to reach the target. For the therapy sessions with the hand module C integrated on the shoulder-elbow module B, targets will be presented sequentially. For the therapy sessions with the wrist module B, the targets will be presented randomly. Some participants may find use of the hand module C physically too challenging. In this situation, therapy with the shoulder-elbow module A and randomly presented targets will be used instead of the hand module C.
Figure 2 summarises the robot assisted training programme.

Figure 2: Summary of robot assisted training



Robotic kinematic (motion and movement) and kinetic (force) evaluations will be incorporated into every third training session. These evaluations monitor participant performance and will

be used to give feedback and encouragement.

The robot assisted training sessions will be provided by a therapy assistant with supervision from a senior therapist. The senior therapist will review a participant's first session on both the shoulder/elbow robot module and wrist module to ensure correct positioning and familiarisation with robot. The senior therapist will review participants at their last session on each robot module to provide a summary of their training and to give feedback at the end of treatment. The senior therapist will also provide supervision and support for the therapy assistant as required. The senior therapist and therapy assistant will receive training on the use of the InMotion robot gym system and the robot programmes to be followed for the study. A RATULS robot assisted training manual will also be provided for therapy staff involved in the study.

All participants randomised to robot assisted training will also receive:

i. A participant information sheet which provides further detail about the robot assisted training programme.

ii A study 'arm rehabilitation therapy log' where they will be asked to record each robot assisted training session and any 'usual' upper limb rehabilitation that they receive during the course of the study. This booklet will also contain a short section to collect participant feedback about robot assisted training. Participants will be asked to bring these documents to the outcome assessment visits for collection (the external appearance of these documents is the same in each treatment group to avoid unblinding the outcome assessor). Participants will also receive periodic text messages to remind them to complete their arm rehabilitation log.

iii. A participant newsletter at 2 and 5 months post randomisation. These newsletters will give general information about the study, reminders about study procedures and updates on trial progress. Any general interest news about stroke may also be included as available.

Transport to and from robot assisted training sessions will be provided for participants and carers as required.

Group 2: Enhanced upper limb therapy programme

Group 2 will receive an enhanced upper limb therapy programme provided for up to 45 minutes per day, three days per week for 12 weeks, in addition to usual care. One hour will be allowed for each therapy session to facilitate preparation and set up.

Participants with no active upper limb function will receive therapy which aims to improve and maintain range of movement, encouraging active assisted upper limb movement in the context of functional activities, along with hand hygiene and positioning. Participants with some retained active upper limb movement will concentrate on task-orientated practice aimed at patient-centred goals.

The therapy sessions will be provided by a therapy assistant with supervision from a senior therapist. A senior therapist will assess/review each participant at baseline, four, eight and 12 weeks and plan/adjust the programme according to individual progress and need. The senior therapist will also provide supervision and support for the therapy assistant as required. The senior therapist and therapy assistant will receive training to deliver the enhanced upper limb therapy programme and a RATULS enhanced upper limb therapy manual will be provided.

All participants randomised to enhanced upper limb therapy will also receive:

i. A participant information sheet which provides further detail about the enhanced upper limb therapy programme.

ii. A study 'arm rehabilitation therapy log' where they will be asked to record each study therapy session and any 'usual' upper limb rehabilitation that they receive during the course of the study. This booklet will also contain a short section to collect participant feedback about the study enhanced upper limb therapy. Participants will be asked to bring these documents to the outcome assessment visits for collection (the external appearance of these documents is the same in each treatment group to avoid unblinding the outcome assessor). Participants will also receive periodic text messages to remind them to complete their arm rehabilitation log.

iii. A participant newsletter at 2 and 5 months post randomisation. These newsletter will give general information about the study, reminders about study procedures and updates on trial progress. Any general interest news about stroke may also be included as available.

Transport to and from enhanced upper limb therapy sessions will be provided as required.

Group 3: Usual care

Group 3 will receive usual care. Defining usual care is a challenge for any stroke rehabilitation trial. One of the current NICE quality standards is that 'patients with stroke are offered a minimum of 45 minutes of each active therapy that is required for a minimum of five days a week, at a level that enables the patient to meet their rehabilitation goals for as long as they are continuing to benefit from therapy and as long as they are able to tolerate it'[29]. For most stroke services this is aspirational and the majority of patients do not receive this intensity[30] particularly after discharge from hospital or early supported discharge services. Patients with chronic stroke are unlikely to receive ongoing rehabilitation in the longer term. Most services do not regularly review patients to address unmet rehabilitation needs beyond one year.

All participants randomised to usual care will also receive:

i. A participant information sheet which provides further detail about the importance of a 'usual care' group in a clinical trial.

ii. A study 'arm rehabilitation therapy log' where they will be asked to record any 'usual' upper limb rehabilitation that they receive during the course of the study. Participants will be asked to bring these documents to the outcome assessment visits for collection (the external appearance of these documents is the same in each treatment group to avoid unblinding the outcome assessor). Participants will also receive periodic text messages to remind them to complete their arm rehabilitation log.

iii. A participant newsletter at 2 and 5 months post randomisation. These newsletter will give general information about the study, reminders about study procedures and updates on trial progress. Any general interest news about stroke may also be included as available.

Outcome assessments

Outcomes will be assessed at three months (+/- 7 days) and six months (+/- 7 days) following randomisation.

Assessments will be undertaken in two stages:

Stage 1 will be a self completion postal questionnaire consisting of the Stroke Impact Scale[20] (three and six months), and the adapted Client Services Receipt Inventory[26-28] resource utilisation questions (six months only). The questionnaires will be posted by LCRN staff or a local study administrator at a study hub (according to local preference) one week prior to the stage 2 assessment. Participants will be asked to bring the completed questionnaire to the stage 2 appointment.

Stage 2 will be a face to face assessment with a researcher blinded to randomisation group. The researcher will answer any queries about the stage 1 questionnaire and check it for completeness. If the questionnaire is not returned, the researcher will provide the participant with another copy and assist with completion. The researcher will then ask the participant to undertake the following assessments: Barthel ADL Index[18, 19], EQ-5D-5L[21], ARAT[16], Fugl-Meyer Test[17] (motor and sensory arm sections), and ask about adverse events. At the end of the six month stage 2 assessment, participants will be given a further self-completion questionnaire and be asked to return this by post to the local study co-ordinator/LCRN staff. A pre-paid envelope will be provided. This questionnaire contains time and travel resource use questions[31, 32]. Postal reminders to complete this questionnaire will be sent after two and four weeks if it has not been returned.

The stage 2 assessment will take place at the study hub, a study spoke site or in the participant's home according to local preference. The local study administrator/LCRN staff will arrange the appointment and transport for the participant if required. If a participant is not contactable, the study staff will ring him/her on two further occasions over the next seven days. One of these calls will be in the evening if the person may be working. If there is still no response the staff will contact the general practice surgery to check the contact details and see if he/she has died. Data about use of services prior to death will be collected from health records by LCRN staff as appropriate.

All study participants will receive a thank you letter from the RATULS study team on completion of their involvement in the trial. Letters will be posted by the local study administrator/LCRN staff following the six month outcome assessment.

Staff training

All staff involved in the study will receive study specific training. Staff performing study assessments (screening, baseline, outcomes) and delivering study interventions will receive specific training in these aspects. In addition, manuals describing delivery of the interventions and instructions on how to perform the assessments will be provided. Where possible, video demonstrations will also be prepared and made available for on-going reference.

Blinding

Due to the nature of the interventions, it will not be possible to blind participants or treating therapists to treatment allocation. Stage 2 outcome assessments will be conducted by a researcher blinded to treatment allocation. At each outcome assessment the researcher will be asked to record whether they have unintentionally become aware of treatment allocation due to conversation with the participant. Success of outcome assessment blinding will be reported.

Study withdrawal

No specific withdrawal criteria have been pre-set. Participants may withdraw from the study at any time for any reason. If a participant wishes to discontinue robot assisted training or the enhanced upper limb therapy, they will be encouraged to remain in the study for the purposes of data collection in line with the study schedule. Data collected prior to withdrawal will be used in the study analysis unless consent for this is specifically withdrawn. Should a decision to withdraw from the study be made, a reason for withdrawal will be sought but participants can chose to withdraw without providing an explanation.

Investigators, GPs, stroke physicians and therapists may also withdraw participants from the study at any time if they feel it is no longer in their interest to continue, for example, because of intercurrent illness or adverse events. Withdrawal may be from study treatments and/or assessments. Where possible, participants discontinuing study treatments will continue in the study for follow up assessments.

If a participant permanently loses capacity to consent to research during their participation in the study, they will be withdrawn. Data collected prior to withdrawal will be used in the study analysis.

Safety evaluation

The safety of robot assisted training, enhanced upper limb therapy and usual care will be evaluated by examining the occurrence of all adverse events and serious adverse events in accordance with National Research Ethics Committee (NRES) guidance for non CTIMP trials.

Definitions

Adverse event (AE): Any untoward medical occurrence in a participant to whom a study intervention or procedure has been administered, including occurrences which are not necessarily caused by or related to that intervention. An AE, therefore, does not necessarily have a causal relationship with the treatment. In this context, "treatment" includes all interventions (including comparative agents) administered during the course of the study. Medical conditions/diseases present before starting study treatment are only considered adverse events if they worsen after starting study treatment.

Related AE: An AE that results from administration of any of the research study procedures. All AEs judged by either the reporting investigator or the sponsor as having reasonable causal relationship to a study procedure qualify as 'related adverse events'. The expression "reasonable causal relationship" means to convey in general that there is evidence or argument to suggest a causal relationship.

Causality: The assignment of the causality should be made by the investigator responsible for the care of the participant. All adverse events judged as having a reasonable suspected causal relationship to a study procedure are considered to be related adverse events. If any doubt about the causality exists, the local investigator (PI) should inform the Chief Investigator. In the case of discrepant views on causality between the investigator and others, all parties will discuss the case. In the event that no agreement is made, the main REC and other bodies will be informed of both points of view.

Serious Adverse Event (SAE): an untoward occurrence that:-

- Results in death
- Is life-threatening (refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires hospitalisation, or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Consists of a congenital anomaly or birth defect
- Is otherwise considered medically significant by the investigator

Medical judgement should be exercised in deciding whether an AE is serious in other situations. Important medical events that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

Unexpected Adverse Event: An adverse event that is not an expected occurrence in the circumstances of this study.

Recording and reporting of adverse events

All adverse events will be recorded. This will occur for the duration of a participant's involvement in the study. Recording will take place at the study outcome assessments by including the following questions in the outcome proforma: "are there any new medical problems since the last study assessment?" In addition, we will specifically enquire about upper limb pain.

Events considered to be SAEs will subsequently be documented onto a separate study SAE form, and a causality and expectedness assessment will be performed. As study investigators or other members of the research team may become aware of SAEs at times other than at outcome assessment appointments, the SAE form will also be used to directly capture these events.

Initial/provisional SAE reports can be made by telephone or email to the study co-ordinating centre. All initial/provisional reports must be followed by a fully completed SAE form. If incomplete information is available at the time of this initial report, further information must be provided on a follow up form as soon as it is available. All SAEs regardless of causality or expectedness will be reported to the Chief Investigator and trial sponsor (Newcastle upon Tyne Hospitals NHS Foundation Trust) in line with local policies. The main REC will be notified of related and unexpected SAEs within 15 days of the Chief Investigator becoming aware of the event. AE data will be processed with routine study data.

Statistical analysis

Primary analysis

The primary outcome measure is the ARAT[16] at three months. It has been suggested that the minimal clinically important difference for the ARAT is 10% of its range (6 points)[33] but a smaller treatment effect may be clinically beneficial in those with severe initial upper limb functional limitation who are likely to improve less than those with more moderate limitation. There will be a stepped approach to define 'successful outcome': baseline ARAT 0-7 must improve by three or more points; baseline ARAT 8-13 improve by four or more points; baseline ARAT 14-19 improve by five or more points; baseline ARAT 20-39 improve by six or more points. Analyses will be by intention-to-treat. Logistic regression will be used to compare the primary outcome (success) between the three randomisation groups at three and six months, adjusting for any imbalance in key covariates. The use of multi-level logistic models will be explored. It may be possible to fit 3-level models (hubs, spokes and participants), but since there are only four centres with a hub, and up to four stroke services accessing an InMotion robotic gym system at each hub, it may be necessary to fit a 2-level model (stroke services and participants).

Secondary analyses

The secondary outcomes will be compared between the three groups at three and six months using multi-level linear regression adjusting for baseline values and key covariates.

We will consider any difference in attrition rates, and any non-randomness of the attrition, when comparing outcomes between the three groups. The pattern of missing observations because of loss to follow-up will be examined to determine both the extent of missingness, and whether it is missing at random or is informative. If data is missing to a sufficient extent, the use of appropriate multiple imputation techniques will be considered. Although mortality is possible within the six month follow-up period, it is thought to be sufficiently uncommon that methods for joint modelling of survival and longitudinal data will not be necessary.

Further descriptive analyses will explore the relationship between the severity of baseline upper limb function and time since stroke upon the effectiveness of the intervention. There is not sufficient power to perform any formal subgroup analyses. The time pattern of upper limb recovery will be explored by extending the earlier multi-level models to include a further within-patient level (ARAT scores collected at baseline, 3 and 6 months). However, this will depend on the relationship being approximately linear.

Sample size

The sample size is 762 participants (254 participants per group). Responses from 216 participants in each randomisation group will provide 80% power (significance level of 1.67% because of multiple comparisons) to detect a 15% difference in ‘successful outcome’ between

each of the three pairs of treatments (robot assisted training, enhanced upper limb therapy, usual care). We have allowed for 15% attrition and inflated the sample size to 762 participants. Reasons for loss from the trial will be recorded.

Economic analysis

The economic analysis will include a detailed micro costing analysis. This will be based upon both a 'within trial' analysis and a modelling exercise to explore cost impact over the longer term. Data collection from the trial will focus on estimating the cost of the interventions. Analyses will be carried out from the perspective of the NHS and personal and social services, but we will also take a societal perspective by including costs borne by the participants and their informal carers. All relevant costs associated with providing the interventions will be measured, this will include the cost of using the InMotion robotic gym system, costed on a per patient basis. All costs will be derived using routine data sources[34] and study specific estimates. Where appropriate, discounting will be applied to costs and outcomes[35]. Costs in the follow-up period will also be taken into account, this includes secondary care resource e.g. inpatient stays and outpatient visits; primary care resource use e.g. general practice, therapy visits and prescription costs. These data will be collected using a health service utilisation questionnaire (adaption of the Client Services Receipt Inventory[26-28]) administered six months post-randomisation. Patient costs will also be collected via a time and travel questionnaire, based upon one successfully used in a number of NIHR HTA funded trials[31, 32]. This will include questions relating to travel time, time away from employment (if appropriate) and time spent providing care. The within trial analysis will also compare changes in health related quality of life, based on responses to the EQ-5D-5L at baseline, three and six months post randomisation. These data will be combined with study participant's mortality to estimate quality adjusted life years (QALYs). This measure provides a profile of quality of life over time. The results of the analyses will be presented as point estimates of mean incremental costs and QALYs. Techniques such as bootstrapping will be used alongside deterministic sensitivity analyses to address uncertainty[36]. In addition, a within trial cost-utility analysis will be performed where both costs and QALY data will be combined into an incremental cost per QALY. The cost-utility analysis will include deterministic and stochastic sensitivity analysis, presented as point estimates and cost-effectiveness acceptability curves (CEACs).

An economic model will also be developed to assess the cost and health consequences measured in terms of QALYs of stroke recovery beyond the six month timeframe of the trial. The data from the trial will be the main source of data for this model but further data with which to model outcomes beyond a six month follow-up will be systematically derived from the literature and other existing data sources following guidance for best practice[37]. These data will include information on factors such as the incidence of hospitalisation and the need for residential/nursing home care, beyond the trial follow-up period. Sensitivity analysis will be applied to the model using probabilistic and deterministic sensitivity analyses to address parameter and other forms of uncertainty. The data on both costs and QALYs for both trial and model based analyses will be reported separately.

Parallel process evaluation

Alongside the RCT, a two stage process evaluation will be conducted to understand both (i) participants' and health service professionals' experiences of robot assisted training; enhanced upper limb therapy and usual care and (ii) factors affecting the implementation of the trial within and across study sites. The process evaluation will capture data concerning feasibility and accumulating experience of the therapies being provided. In stage one data collection will be by semi-structured interview using a pre-developed and piloted interview schedule. Data collection in stage two will be primarily by interview, however, analysis will also draw upon trial data including baseline, therapy and outcome (3 and 6 month) assessments. Interviews will primarily be conducted face-to-face, however, due to the geographical spread of the study sites, some follow-up interviews will be conducted by telephone for efficiency (these are

particularly appropriate for health service professionals). Data collection and analysis relating to study of implementation factors will be informed by Normalization Process Theory (NPT)[39].

Participant study group

In stage one a sub-set of approximately 25-30 study participants will be recruited across study sites, to achieve a maximum variation sample, ensuring representation of participants differing in terms of key factors such as randomisation group, clinical severity and time from stroke. Participants in the robot assisted training and enhanced upper limb therapy programme groups will be invited to be interviewed on two occasions: (1) soon after therapy commences; and (2) towards the end of the 12 week therapy period, to determine how perceptions of acceptability of therapy may change over time.

In stage two approximately 25 study participants will be recruited, again with the aim of achieving maximum variation in the sample. Participants in the treatment groups will be interviewed twice. However, in this stage, time points are (1) towards the end of the twelve week therapy, and (2) around the 6 month follow-up assessment, to provide insight into their experience of trial participation, and the impact of the therapy they received, post treatment. In addition, the baseline, therapy and outcome assessment data will be reviewed descriptively, for the participants who have been interviewed as part of stage two. This will allow comparison of trial participants' assessment data with their subjective experiences of participating in the trial, to inform later interpretation of the results of the trial.

Participants to be invited for interview will be identified from the study database (containing data held by unique study number only) by the researcher conducting the interviews. The researcher will advise the local study centre co-ordinators/administrators of the selected participant numbers and the local study co-ordinator/administrator/LCRN staff will mail a letter of invitation, an information sheet and a self completion contact details form for the participant to return directly to the researcher if they are interested in taking part in the interview(s). After one week non responders will be reminded about the invitation. This will be either by face to face contact with the local study centre co-ordinator/administrator (some patients may regularly see the local study co-ordinator/administrator if they are attending the study hub for robot or enhanced therapy) or by telephone. It will be presumed that participants not responding after this reminder do not wish to take part in the interviews.

The researcher will telephone the responding participants, go over the purpose of the interview(s) and agree a mutually convenient time for a first interview to take place. Prior to any potential second interview, participants will be re-contacted by the researcher to check that they are still willing to take part in the second interview. Consent to be interviewed will be obtained in writing prior to commencement of each interview.

Health service professional study group

A sample of approximately 20 health service professionals will be recruited across study sites and study groups. Interviews will take place in both stage one and stage two of the process evaluation. The aim will be to interview a range of health service professionals e.g. senior therapists, therapy assistants, study administrators, principal investigators and NIHR LCRN staff to gain insight into different aspects of the trial including implementation of the robot assisted training, enhanced upper limb therapy and usual care practices, and implementation of the trial itself, including the recruitment and follow-up processes.

Staff to be invited for interview will be identified by the local study centre co-ordinator and/or local study investigators. Each selected member of staff will receive a letter of invitation and an information sheet. Following issue of the invitation letter and information sheet, the researcher conducting the interviews will contact the selected staff to go over the purpose of the interviews and ascertain willingness to take part. A mutually convenient time and place for the interview(s) will be agreed. Consent to be interviewed will be obtained in writing prior to commencement of each interview.

Interview data analysis

Interviews will be audio-taped with the respondents' consent, and transcribed. Data will be mostly analysed using the constant comparative method of qualitative analysis[38] facilitated by analysis software (QSR Nvivo). For a subset of the process evaluation data – that specifically focused on questions concerning implementation - a theory-based approach to analysis will be undertaken[39]. All data analysis will include a proportion of data to be analysed collectively in 'data clinics' where the research team share and exchange interpretations of key themes emerging from the data. A larger proportion of data, however, will be independently thematically coded and compared between two researchers to ensure consistency in the interpretation of data within a broader thematic framework developed as data collection progresses.

Internal pilot study

This study will commence as an internal pilot trial. Two or more hub sites and up to three corresponding spoke sites will be set up, and participant recruitment and treatment will be monitored for nine months. If the internal pilot trial is considered a success, the full trial will continue. The internal pilot will be considered a success if:

i) the study has recruited a minimum of 22 participants (80% of predicted recruitment at month nine);
ii) participants randomised to robot assisted training and enhanced upper limb therapy have received a minimum of 60% of the treatment sessions that are due;
iii) outcome assessments have been conducted according to protocol.

Ethics and regulatory issues

The study sponsor is Newcastle upon Tyne Hospitals NHS Foundation Trust. The study will be conducted in accordance with Research Governance Framework for Health and Social Care[40]. Ethical and NHS Trust approvals will be sought. The study coordinating centre will require a written copy of local approval documentation before initiating each participating site and accepting participants into the study.

Confidentiality

Personal data will be regarded as strictly confidential. Original paper case record forms containing study data will be stored in the investigator site file at each research site. All study files will be securely stored and access restricted to staff involved in the study. Research staff at sites will enter data from paper forms onto a secure web-based electronic database run and maintained by Newcastle University. Data will be entered using participant unique study numbers only. Access to this database will be password protected and limited to staff at research sites or Newcastle University who are involved in the study.

The InMotion robotic gym computers will store data from each participant session. Data will be stored by unique study number only. Periodically, this data will be copied from the robot computer system into an electronic database maintained by Newcastle University. This may involve transfer by external hard drive, or it may be possible to develop an online database and upload the data directly to this database from the robotic computer.

The study will comply with the Data Protection Act 1998, and Caldicott Guardian approval for use of patient identifiable data will be sought in line with local requirements. All trial documentation will be retained for future audit and inspection in line with the sponsor policies.

Trial monitoring, quality control and quality assurance

The Chief Investigator will have overall responsibility for study conduct. The Principal Investigators will be responsible for the day-to-day study conduct at their individual sites.

The trial will be managed by a co-ordinating centre based at Newcastle University who will provide day-to-day support for the sites and provide training through investigator meetings, site initiation visits and routine monitoring visits. A Trial Management Group (TMG) will be convened and meet regularly during the study.

Quality control will be maintained through adherence to Newcastle Biomedicine Clinical Research Platform SOPs, the study protocol and research governance regulations. General monitoring of study conduct and data collected will be performed by a combination of central review and site monitoring visits. The main areas of focus will include consent, serious adverse events and essential documents in study files. All monitoring findings will be reported and followed up with the appropriate persons in a timely manner.

A Trial Steering Committee (TSC) will be convened. This will comprise of an independent chair, at least two other independent members, a patient and/or a carer representative and the Chief Investigator. The TSC will agree a charter of operation and meet at least annually during the study. Representatives from NIHR HTA and the study sponsor will be invited to attend TSC meetings.

An independent Data Monitoring and Ethics Committee (DMEC) will be convened to undertake independent review. This will comprise of 3-4 independent members including expert healthcare professionals and a statistician. The purpose of this committee will be to monitor efficacy and safety endpoints. Only the DMEC will have access to unblinded outcome data before the trial ends. The DMEC will agree a charter of operation and meet at least annually during the study.

The study may be subject to inspection and audit by Newcastle upon Tyne Hospitals NHS Foundation Trust under their remit as sponsor.

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Indemnity

NHS Trusts participating in the study have liability for clinical negligence that harms individuals toward whom they have a duty of care. NHS indemnity covers NHS staff and academic staff with honorary contracts conducting the trial for potential liability in respect of negligent harm arising from the conduct of the study. Newcastle upon Tyne Hospitals NHS Foundation Trust is the Sponsor and through the Sponsor, NHS indemnity is provided in respect of potential liability and negligent harm arising from study management. Indemnity in respect of potential liability arising from negligent harm related to study design is provided by NHS schemes for those protocol authors who have their substantative contracts of employment with the NHS and by Newcastle University Insurance schemes for those protocol authors who have their substantive contract of employment with the university. This is a non-commercial study and there are no arrangements for non-negligent compensation.

Dissemination of results

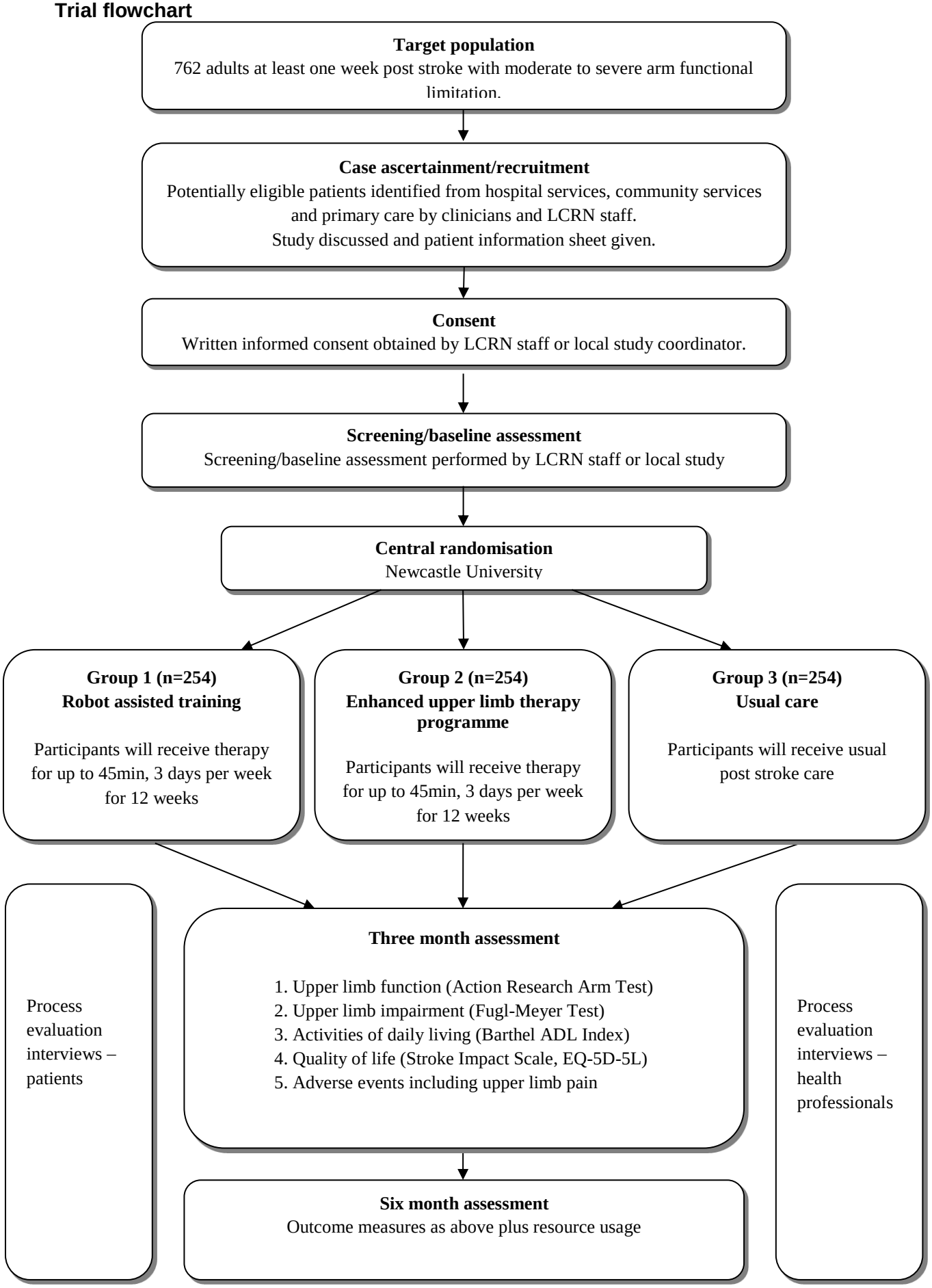
The data will be the property of the Chief Investigator and Co-Investigator(s). Publication will be the responsibility of the Chief Investigator.

The study will be presented at national and international conferences, and reported in peer reviewed journals and a HTA monograph. Reports will be written for the study sponsor and regulatory bodies. A summary of the results will be sent to study participants.

Anonymised data will be provided to research databases as requested (e.g. the Cochrane

Collaboration, the Virtual International Stroke Trials Archive (VISTA)) to enable future meta-analyses. Anonymised robot kinematic and kinetic data will be provided to Co-Investigators for exploratory analyses.

Trial flowchart



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Appendix 1: Summary of study schedule

	Initial study approach	Further study details	Screening assessment	Baseline assessment	Outcome assessment 1 (3 month)	Outcome assessment 2 (6 month)
Study invitation/discussion and PIS given	x					
Informed consent		x				
Contact details			x			
Demography			x			
Details of stroke			x			
Medical history			x			
Upper limb function (Action Research Arm Test)			x		x	x
Cognition assessment (Montreal Cognitive Assessment)				x		
Language assessment (Sheffield Aphasia Screening Test)				x		
Upper limb impairment (Fugl-Meyer Motor and Sensory Scale (arm section))				x	x	x
Activities of daily living assessment (Barthel ADL Index)				x	x	x
Quality of life assessment (EQ-5D-5L)				x	x	x
Impact of stroke assessment (Stroke Impact Scale)					x	x
Upper limb pain (numerical rating scale)				x	x	x
Randomisation				x		
Issue of study arm rehabilitation logs				x	x	
Resource utilisation				x		x
Adverse Events					x	x

Appendix 2: Project Gantt chart

ID	Task Name	Start	Finish
1			
2	**PHASE 1: PRE-PROJECT WORK**	**01/10/2012**	**31/12/2013**
3	Develop detailed manuals for robot assisted training and enhanced therapy programme	01/10/2012	30/09/2013
4	Finalise study protocol	01/01/2013	30/04/2013
5	Prepare study documentation required for REC	01/01/2013	30/04/2013
6	Prepare and submit REC application (via IRAS)	01/01/2013	30/04/2013
7	Prepare and submit global R&D application (via IRAS)	01/01/2013	30/04/2013
8	Await REC and global R&D approvals	01/05/2013	31/07/2013
9	Prepare remaining study documentation	01/05/2013	31/12/2013
10	Recruit TSC and DMEC members	03/06/2013	31/12/2013
11	Agree NHS costs at eight pilot sites (2 hubs, 6 spokes)	01/10/2012	31/12/2013
12	Negotiate logistics at 8 pilot sites	01/10/2012	31/12/2013
13			
14	**PHASE 2: INTERNAL PILOT TRIAL**	**01/01/2014**	**31/12/2014**
15	Submit and await R&D (SSI) applications/approvals for eight pilot sites	01/01/2014	30/06/2014
16	Set up study randomisation service	01/01/2014	31/03/2014
17	Set up study online data entry system	01/01/2014	31/03/2014
18	Recruit and train staff at two pilot hubs	01/01/2014	31/03/2014
19	Recruit and train staff at six pilot spokes	01/02/2014	30/06/2014
20	Pilot sites recruitment (commencing study hubs, adding study spokes monthly)	01/04/2014	31/12/2014
21	Pilots sites qualitative interviews	01/06/2014	30/11/2014
22	Review success of internal pilot trial	01/10/2014	31/12/2014
23	Agree NHS costs at additional eight sites (hubs 3 & 4, spokes 7 - 12)	01/01/2014	31/12/2014
24			
25	**PHASE 3: MAIN TRIAL**	**01/01/2015**	**31/08/2019**
26	Continued recruitment sites 1-8	01/01/2015	31/08/2018
27	Submit and await R&D (SSI) applications/approvals for eight sites (hubs 3 & 4, spokes 7-12)	01/01/2015	30/06/2015
28	Recruit and train staff at hubs 3 & 4	01/01/2015	31/03/2015
29	Recruit and train staff at spokes 7 - 12	01/02/2015	30/06/2015
30	Recruitment sites 9 - 16 (commencing study hubs, adding study spokes monthly)	01/04/2015	31/08/2018
31			
32	Total participant recruitment pilot/main trial	01/04/2014	31/08/2018
33	Provision of study interventions pilot/main trial	01/04/2014	30/11/2018
34	12 week outcome assessments	01/07/2014	30/11/2018
35	6 month outcome assessments	01/10/2014	28/02/2019
36	Main trial qualitative interviews	01/03/2017	31/10/2017
37	Research site governance monitoring	01/04/2014	28/02/2019
38			
39	**Data Handling and Reports**	**01/04/2014**	**31/08/2019**
40	Data monitoring and cleaning	01/04/2014	31/03/2019
41	Final data analyses	01/04/2019	30/06/2019
42	HTA final report writing	04/04/2019	31/08/2019
43	REC Annual Reports	01/01/2014	30/11/2018
49	HTA 6 Monthly Reports	01/07/2014	31/07/2019
61			
62	**MEETINGS**	**01/10/2012**	**31/08/2019**
63	**Applicant Group Meetings**	**01/10/2012**	**31/08/2019**
78	**TSC Meetings**	**01/01/2014**	**31/08/2019**
91	**DMEC Meetings**	**01/01/2014**	**31/08/2019**
104	**Trial Management Group Meetings**	**01/10/2012**	**31/08/2019**