Robot-assisted training compared with an enhanced upper limb therapy programme and with usual care for upper limb functional limitation after stroke: the RATULS three-group RCT

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Scientific summary

The RATULS 3-group RCT

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Scientific summary

Background

Upper limb problems occur in approximately 80% of people who have experienced an acute stroke, and 50% of stroke survivors continue to have upper limb motor impairment 4 years post stroke. This can cause difficulties with activities of daily living, such as washing and dressing, and lowers quality of life. Improving upper limb function post stroke is a top 10 research priority for stroke survivors, carers and clinicians.

It is unclear how to optimise stroke patients' upper limb recovery. Systematic reviews suggest that patients benefit from therapy programmes in which they repeatedly practise functional tasks. A Cochrane overview of systematic reviews (Pollock A, Farmer SE, Brady MC, Langhorne P, Mead GE, Mehrholz J, Van Wijck F. Interventions for improving upper limb function after stroke. *Cochrane Database Syst Rev* 2014;**11**:CD010820) found moderate-quality evidence that arm function after a stroke can be improved by the provision of at least 20 hours of additional repetitive task training.

Robot-assisted training enables patients to perform repetitive task training and is a promising treatment for improving arm function after stroke. However, to date, studies vary in patient characteristics, devices used, duration and amount of training, control group and outcome measures used. Currently, there is no clear evidence for the benefit of robot-assisted arm training over conventional therapy when delivered at the same frequency and duration.

The Robot-Assisted Training for the Upper Limb after Stroke (RATULS) randomised controlled trial evaluated robot-assisted training, compared with an enhanced upper limb therapy programme of the same frequency and duration, and with usual post stroke care.

Aim and objectives

The aim of the RATULS trial was to determine whether or not robot-assisted training with the Massachusetts Institute of Technology-Manus robotic gym system (InMotion commercial version, Interactive Motion Technologies, Inc., Watertown, MA, USA) improved upper limb function post stroke.

The objectives were to:

- determine whether or not robot-assisted training improved upper limb function post stroke, compared with an enhanced upper limb therapy programme or usual care
- determine whether or not robot-assisted training improved upper limb impairment, activities of daily living and quality of life, compared with an enhanced upper limb therapy programme or usual care
- model costs of robot-assisted training, compared with an enhanced upper limb therapy programme or usual care
- seek the views and experiences of patients and health service professionals about the upper limb rehabilitation that they received or provided, and about factors affecting the implementation of the trial
- explore the time pattern of upper limb recovery of participants in each treatment group, and the impact of the severity of baseline upper limb function and time since stroke on the effectiveness of the interventions.

Methods

This was a three-group, pragmatic, observer-blind, multicentre randomised controlled trial with an embedded economic analysis and process evaluation.

Setting

The trial was conducted in four NHS centres in the UK. Each centre comprised a hub site, which was a stroke service in an NHS hospital with a Massachusetts Institute of Technology-Manus robotic gym system, plus several participant identification spoke sites, which were stroke services in adjacent NHS trusts and community services.

Participants

Adults with a first-ever stroke were eligible to take part if they were between 1 week and 5 years post stroke and had moderate or severe upper limb functional limitation (Action Research Arm Test score of 0–39) due to their stroke.

Randomisation

A central independent web-based service hosted by Newcastle University Clinical Trials Unit was used. Participants were stratified according to trial centre, time since stroke (< 3 months, 3–12 months or > 12 months) and severity of upper limb functional limitation (Action Research Arm Test score: 0–7, 8–13, 14–19 and 20–39), and randomised, using permuted block sequences, 1 : 1 : 1 to receive robot-assisted training, the enhanced upper limb therapy programme or usual care.

Trial intervention treatments

Robot-assisted training

This was delivered using the Massachusetts Institute of Technology-Manus robotic gym. Robot-assisted training involved 45 minutes of face-to-face therapy per day, within a 1-hour session, 3 days per week for 12 weeks, and was in addition to usual care.

The enhanced upper limb therapy programme

The enhanced upper limb therapy programme was based on best evidence using repetitive functional task practice to work towards patient-centred goals. Enhanced upper limb therapy involved 45 minutes of face-to-face therapy per day, within a 1-hour session, 3 days per week for 12 weeks, and was in addition to usual care.

Trial control treatment

The control treatment was usual post-stroke NHS care.

Data collection and outcome measures

Eligibility was assessed at a screening assessment, during which the following data were collected: demography, stroke details and upper limb function (measured using the Action Research Arm Test). The following baseline assessments were completed for patients fulfilling the eligibility criteria: stroke severity (measured using the National Institutes for Health Stroke Scale), cognitive function (measured using the Montreal Cognitive Assessment), language skills (measured using the Sheffield Screening Test for Acquired Language Disorders), upper limb impairment [measured using the Fugl-Meyer Assessment (total upper extremity score)], activities of daily living (measured using the Barthel Activities of Daily Living Index), quality of life (measured using the EuroQol-5 Dimensions, five-level version), upper limb pain (measured using a numeric rating scale) and current upper limb rehabilitation treatments. Participants were given a self-completion questionnaire containing pre-trial resource use questions (an adaption of the Client Services Receipt Inventory).

Outcome data were collected at 3 and 6 months post randomisation, and collection was undertaken in two stages:

- Stage 1 was a self-completion postal questionnaire consisting of the Stroke Impact Scale (at both 3 and 6 months), and the adapted Client Services Receipt Inventory resource use questions (at 6 months only).
- Stage 2 was a face-to-face assessment by a researcher masked to the randomisation group who collected the following data: Action Research Arm Test, Fugl-Meyer Assessment (total upper extremity score), Barthel Activities of Daily Living Index, EuroQol-5 Dimensions, five-level version, upper limb pain and adverse events. At the end of the 6-month stage 2 assessment, participants were given a further self-completion questionnaire that included time and travel resource use questions, and were asked to return this by post.

Sample size

The target sample size was 762 participants (254 per group). Responses from 216 participants in each randomisation group would provide 80% power (significance level of $5\% \div 3 = 1.67\%$ because of multiple comparisons) to detect a 15% difference in upper limb functional recovery 'success' (assessed using the Action Research Arm Test) between each of the three pairs of treatments (robot-assisted training, enhanced upper limb therapy and usual care). The baseline estimate of 'success' was estimated as 30% based on outcomes in the National Institute for Health Research Health Technology Assessment programme Botulinum Toxin for the Upper Limb after Stroke trial [Shaw L, Rodgers H, Price C, Van Wijck F, Shackley P, Steen N, *et al.* BoTULS: a multicentre randomised controlled trial to evaluate the clinical effectiveness and cost-effectiveness of treating upper limb spasticity due to stroke with botulinum toxin type A. *Health Technol Assess* 2010;**14**(26)], with a difference of between 45% and 30% corresponding to an odds ratio of 1.9. The sample size was increased during the course of the trial to allow for higher attrition.

Statistical analysis

Analyses were carried out on an intention-to-treat basis, retaining participants in their randomisation groups and including all participants who were not missing data on scale totals or subtotals after simple imputation. Logistic regression was used to compare upper limb functional recovery 'success' (the primary outcome) between the three randomisation groups at 3 months, adjusting for time since stroke, baseline upper limb function (Action Research Arm Test) and trial centre. The secondary outcome of upper limb functional recovery 'success' at 6 months was analysed as for the primary outcome.

Numeric secondary outcomes were analysed at 3 and 6 months using linear regression, adjusting for time since stroke, baseline score and trial centre. Bias-corrected and accelerated confidence

intervals (100,000 bootstrap intervals) are presented for all numerical secondary outcomes because of the distribution of the data. The coverage of the confidence intervals was adjusted to account for the three paired comparisons between the randomisation groups. Because the trial was powered on a significance level of 1.67%, the confidence interval coverage used was 98.33% (100% – 1.67%).

Health economic analysis

A within-trial cost–utility analysis was conducted to assess the incremental cost per quality-adjusted life-year gained. The economic valuation took the perspective of the NHS and Personal Social Services, and all costs were reported using 2018 values. Costs were based on the use of primary care, secondary care and social care services over the 6-month trial period. Quality-adjusted life-years were derived from responses to the EuroQol-5 Dimensions, five-level version, questionnaire administered at baseline and at 3 and 6 months. The incremental cost per quality-adjusted life-year for each participant at 6 months was calculated.

A longer-term model was conducted to extrapolate the mean costs and quality-adjusted life-years to 12 months, based on the results of the trial.

Process evaluation

The process evaluation used semistructured interviews to seek the views and experiences of both participants and health service professionals about the upper limb rehabilitation (i.e. robot-assisted training, enhanced upper limb therapy and usual care) that they received or provided, and about factors affecting the implementation of the trial. An inductive thematic analysis of the data was undertaken.

Results

A total of 770 stroke survivors were randomised to the trial: robot-assisted training, $n = 257$; enhanced upper limb therapy, $n = 259$; and usual care, $n = 254$. Baseline demographics and stroke characteristics were balanced between the groups. The mean age of participants was 61 years (standard deviation 14 years), 468 (61%) participants were men and the median time from stroke to randomisation was 240 days (interquartile range 109–549 days).

Robot-assisted training participants attended a median of 35 (interquartile range 31–36) of the intended 36 sessions. Enhanced upper limb therapy participants attended a median of 34 (interquartile range 29–36) of the intended 36 sessions. The median duration of face-to-face therapy for each attended session was 41 minutes (interquartile range 35–47 minutes) for robot-assisted training and 45 minutes (interquartile range 45–45 minutes) for enhanced upper limb therapy.

Primary outcome

At 3 months, 103 out of 232 (44%) participants in the robot-assisted training group, 118 out of 234 (50%) in the enhanced upper limb therapy group and 85 out of 203 (42%) in the usual care group achieved upper limb functional recovery ‘success’. There was little evidence of a difference between the randomisation groups [adjusted odds ratio: robot-assisted training vs. usual care, 1.2 (98.33% confidence interval 0.7 to 2.0); enhanced upper limb therapy vs. usual care, 1.5 (98.33% confidence interval 0.9 to 2.5); and robot-assisted training vs. enhanced upper limb therapy, 0.8 (98.33% confidence interval 0.5 to 1.3)].

Secondary outcomes

At 6 months, 103 out of 221 (47%) participants in the robot-assisted training group, 118 out of 218 (54%) in the enhanced upper limb therapy group and 81 out of 185 (44%) in the usual care group achieved upper limb functional recovery ‘success’.

Some of the many comparisons between pairs of groups on each outcome at 3 and 6 months showed evidence of differences between randomisation groups that were considered to be clinically important:

- Robot-assisted training participants had less upper limb impairment on the Fugl-Meyer Assessment motor subscale than usual care participants at 3 months (adjusted mean difference 2.8, 98.33% confidence interval 0.7 to 5.0), and the difference was sustained at 6 months (adjusted mean difference 2.5, 98.33% confidence interval 0.1 to 5.1).
- Robot-assisted training participants performed less well in the Stroke Impact Scale activities of daily living domain at 3 months than enhanced upper limb therapy participants (adjusted mean difference −4.8, 98.33% confidence interval −9.5 to −0.1).
- Enhanced upper limb therapy participants had less upper limb impairment on the Fugl-Meyer Assessment total upper extremity score and Fugl-Meyer Assessment motor subscale score than usual care participants at 3 months [adjusted mean difference 3.7 (98.33% confidence interval 0.5 to 6.8) and 3.0 (98.33% confidence interval 0.9 to 5.0), respectively]. Enhanced upper limb therapy participants also performed better in Stroke Impact Scale mobility (adjusted mean difference 5.8, 98.33% confidence interval 0.4 to 11.2) and Stroke Impact Scale activities of daily living (adjusted mean difference 5.6, 98.33% confidence interval 0.9 to 10.2) domains at 3 months than usual care participants.

The following results showed statistical evidence of a difference, but were not considered to be clinically important, as the confidence interval did not include the minimum clinically important difference of the scale:

- Participants in the robot-assisted training group performed less well in the Barthel Activities of Daily Living Index at 3 months than participants in the enhanced upper limb therapy group (adjusted mean difference −0.5, 98.33% confidence interval −1.0 to −0.0).
- Participants in the enhanced upper limb therapy group had better upper limb function on the Action Research Arm Test total score (adjusted mean difference 2.5, 98.33% confidence interval 0.0 to 5.1) and performed better on the Stroke Impact Scale hand function domain (adjusted mean difference 7.9, 98.33% confidence interval 2.2 to 13.5) than participants in the usual care group at 3 months. Participants in the enhanced upper limb therapy group also scored higher than usual care participants on the Barthel Activities of Daily Living Index [adjusted mean difference was 0.7 (98.33% confidence interval 0.2 to 1.2) at 3 months and 0.9 (98.33% confidence interval 0.3 to 1.5) at 6 months].

No difference was seen in the pain numeric rating scale tests between all three randomisation groups. Forty-three serious adverse events were reported for 39 participants in the robot-assisted training group, 42 were reported for 33 participants in the enhanced upper limb therapy group and 29 were reported for 20 participants in the usual care group. None of the serious adverse events was considered to be related to a trial intervention.

Health economic evaluation

The unadjusted results of the economic analysis suggest that, on average, usual care was the least costly option at 6 months, at £3785 per participant (standard deviation £5437), with robot-assisted training being the most costly, at £5387 per participant (standard deviation £4054). The mean cost per participant of enhanced upper limb therapy was £4451 (standard deviation £6033). Enhanced upper limb therapy had a higher quality-adjusted life-year gain [0.23 (standard deviation 0.10)] than usual care [0.21 (standard deviation 0.11)] or robot-assisted training [0.21 (standard deviation 0.12)] at 6 months. The incremental cost per quality-adjusted life-year at 6 months for participants in the enhanced upper limb therapy group, compared with those in the usual care group, was £74,100, with a 19% chance of being cost-effective at the £20,000 willingness-to-pay threshold. Throughout the analysis, results suggested that robot-assisted training was more costly than usual care and enhanced upper limb therapy, and was no more effective than enhanced upper limb therapy or usual care.

Process evaluation

Forty-four participants and 35 professionals were interviewed. Despite the intensity of the RATULS trial therapies, participants in both the robot-assisted training and the enhanced upper limb therapy groups generally found the therapies to be acceptable, and were able to complete their therapy programmes. Participants reported a range of benefits in both therapy programmes, and many reported (self-judged) maintenance of some benefits at 6 months.

Delivering the RATULS trial required continuous investment of effort by trial centres and the co-ordinating centre, with high levels of engagement from the professional staff involved. At times, flexibility and adaptation of some of the processes, within the constraints of the trial protocol, were necessary to support continued engagement of participants and professionals.

Conclusion

The RATULS trial did not find evidence that robot-assisted training using the Massachusetts Institute of Technology-Manus robotic gym improved upper limb function after a stroke when compared with an enhanced upper limb therapy programme of the same frequency and duration, or with usual care. Robot-assisted training led to improvement in upper limb impairment, but this did not translate into improvements in other outcomes. However, enhanced upper limb therapy led to potentially clinically important improvements in upper limb impairment, mobility and performance in activities of daily living at the end of the intervention period. Neither robot-assisted training nor enhanced upper limb therapy were cost-effective.

Implications for health care

The results of the RATULS trial do not support the routine use of robot-assisted training (as provided in this trial) for patients with moderate or severe upper limb functional limitation resulting from stroke. There is evidence of potential benefit of enhanced upper limb therapy, although, as delivered in this trial, it is unlikely to be cost-effective at the current standard of willingness to pay for a quality-adjusted life-year (i.e. £20,000).

Implications for research

The RATULS trial has demonstrated that it is feasible to undertake large multicentre trials to evaluate new rehabilitation technologies. Further research is needed to find ways to translate the improvements in upper limb impairment seen with robot-assisted training into improvements in upper limb function and activities of daily living. This might involve combining robot-assisted training with more functionally orientated therapy strategies. Innovations to make enhanced rehabilitation programmes more clinically effective and cost-effective are needed.

Trial registration

This trial is registered as ISRCTN69371850.

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