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Robot-Assisted Therapy for Long-Term Upper-Limb Impairment after Stroke

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Abstract

Background—Effective rehabilitative therapies are needed for patients with long-term deficits after stroke.

Methods—In this multicenter, randomized, controlled trial involving 127 patients with moderate-to-severe upper-limb impairment 6 months or more after a stroke, we randomly assigned 49 patients to receive intensive robot-assisted therapy, 50 to receive intensive comparison therapy, and 28 to receive usual care. Therapy consisted of 36 1-hour sessions over a period of 12 weeks. The primary outcome was a change in motor function, as measured on the Fugl-Meyer Assessment of Sensorimotor Recovery after Stroke, at 12 weeks. Secondary outcomes were scores on the Wolf Motor Function Test and the Stroke Impact Scale. Secondary analyses assessed the treatment effect at 36 weeks.

Results—At 12 weeks, the mean Fugl-Meyer score for patients receiving robot-assisted therapy was better than that for patients receiving usual care (difference, 2.17 points; 95% confidence interval [CI], −0.23 to 4.58) and worse than that for patients receiving intensive comparison therapy (difference, −0.14 points; 95% CI, −2.94 to 2.65), but the differences were not significant. The results on the Stroke Impact Scale were significantly better for patients receiving robot-assisted therapy than for those receiving usual care (difference, 7.64 points; 95% CI, 2.03 to 13.24). No other treatment comparisons were significant at 12 weeks. Secondary analyses showed that at 36 weeks, robot-assisted therapy significantly improved the Fugl-Meyer score (difference, 2.88 points; 95% CI, 0.57 to 5.18) and the time on the Wolf Motor Function Test (difference, −8.10 seconds; 95% CI, −13.61 to −2.60) as compared with usual care but not with intensive therapy. No serious adverse events were reported.

Conclusions—In patients with long-term upper-limb deficits after stroke, robot-assisted therapy did not significantly improve motor function at 12 weeks, as compared with usual care or intensive

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therapy. In secondary analyses, robot-assisted therapy improved outcomes over 36 weeks as compared with usual care but not with intensive therapy. (ClinicalTrials.gov number, NCT00372411.)

Stroke is a leading cause of long-term disability in the United States, affecting an estimated 6.4 million Americans.[1] Long-term disability is often associated with persistent impairment of an upper limb.[2] Despite the development of many programs for recovery after stroke, the effectiveness of rehabilitation in improving functioning and quality of life for patients with deficits more than 6 months after a stroke has not been definitively shown. Robotic rehabilitation devices have the potential to deliver high-intensity, reproducible therapy. Advances in robotics and an increased understanding of the latent neurologic potential for stroke recovery led to our initiation of this multicenter, randomized, controlled trial, called the Veterans Affairs (VA) Robotic-Assisted Upper-Limb Neurorehabilitation in Stroke Patients study, to determine whether a rehabilitation protocol using the MIT–Manus robotic system (Interactive Motion Technologies),[3] as compared with a program based on conventional rehabilitative techniques or usual care, could improve functioning and quality of life of stroke survivors with long-term upper-limb deficits.

METHODS

Study Design

Details regarding the study design and baseline characteristics of the patients have been reported previously.[4] The study was approved by the institutional review board at each medical center and by the human rights committee at the coordinating center. An independent data and safety monitoring board oversaw the conduct, safety, and efficacy of the trial. Sponsorship and oversight were provided by the Veterans Affairs (VA) Cooperative Studies Program, with additional funding from the VA Rehabilitation Research and Development Service. The sponsors reviewed the manuscript before publication but were not responsible for the interpretation of the results or the decision to submit the manuscript for publication. The planning committee designed the trial, the participating investigators collected the data, and the listed authors wrote the manuscript. Study biostatisticians at the coordinating center had full access to the data and vouch for the accuracy and completeness of the analyses. The robotic system and all other rehabilitative equipment were purchased by the Department of Veterans Affairs through the VA Cooperative Studies Program Pharmacy Coordinating Center in Albuquerque, New Mexico. The robot manufacturer had no role in the study.

Study Population

We recruited veterans from four participating VA medical centers who were 18 years of age or older and had long-term, moderate-to-severe motor impairment of an upper limb from a stroke that had occurred at least 6 months before enrollment. Such impairment was defined as a score of 7 to 38 on the Fugl-Meyer Assessment of Sensorimotor Recovery after Stroke,[5] a scale with scores for upper-limb impairment ranging from 0 (no function) to 66 (normal function). All patients provided written informed consent.

Study Interventions

Patients were randomly assigned to receive robot-assisted therapy, intensive comparison therapy, or usual care with the use of a permuted-block design that was stratified according to site. Robot-assisted therapy was administered for a maximum of 36 sessions over a period of 12 weeks (up to 14 weeks to allow for missed sessions).

The robotic system consisted of four modules: a shoulder–elbow unit for horizontal movements; an antigravity unit for vertical movements; a wrist unit for flexion–extension, abduction–adduction, and pronation–supination movements; and a grasp-hand unit for closing and opening movements. The 12 weeks of training consisted of four training blocks and were supervised by a therapist. In the first 3-week block, a planar shoulder-and-elbow training robotic device was used. In the second 3-week block, an antigravity shoulder and grasp-hand device was used. In the third 3-week block, the wrist robot was used. In the final block, all three devices were used to integrate proximal (shoulder) to distal (wrist and hand) training (see video).

Modules were used separately and in combination to perform high-intensity, repetitive, task-oriented movements (1024 per session on average), directed by video screens. Training targeted isolated proximal, distal, and integrated movements of the upper limb. The robot provided assistance if patients were unable to initiate or complete a movement independently.

Intensive comparison therapy consisted of a structured protocol using conventional rehabilitative techniques, such as assisted stretching, shoulder-stabilization activities, arm exercises, and functional reaching tasks. This therapy matched robot-assisted therapy in schedule and in the form and intensity of movements.[4,6] The same research personnel delivered both robot-assisted therapy and intensive comparison therapy at each site.

The usual-care group received customary care available to all patients (i.e., medical management, clinic visits as needed, and in some cases rehabilitation services), which was not dictated by the protocol. Patients in the usual-care group were offered their choice of robot-assisted therapy or intensive comparison therapy after their final study visit.

Outcome Measures

Trained evaluators who were unaware of study-group assignments assessed patients 6, 12, 24, and 36 weeks after randomization. The primary outcome was a change in the Fugl-Meyer score at 12 weeks, as compared with the baseline value. Secondary outcomes were changes in the score on the Wolf Motor Function Test[7,8] and in the score on the Stroke Impact Scale, version 3.0, at 12 weeks, as compared with baseline values.[9] The Wolf Motor Function Test measures proximal and distal upper-limb motor control and consists of two strength measurements and 15 timed functional tasks. The tasks are averaged to produce a score in seconds that ranges from 0 to 120 seconds, with higher scores indicating worse functioning. The Stroke Impact Scale evaluates function and quality of life in eight clinically relevant domains on the basis of self-report. The domains of hand function, activities of daily living, instrumental activities of daily living, mobility, and social participation were

used; scores range from 0 to 100, with higher values indicating better functioning and social participation.

Safety outcomes included the occurrence of adverse events and measures of pain (rated on a scale of 0 to 10, with higher scores indicating more severe pain) and spasticity (rated on the Modified Ashworth Scale,[10] which ranges from 0 to 5, with higher scores indicating more severe spasticity). Site personnel inquired about adverse and serious adverse events at each study contact. Patients did not keep lists or diaries of adverse events.

Cost Analysis

We used the purchase price of each robot (assuming full depreciation over a period of 5 years) to estimate the cost per session of robot-assisted therapy. Therapist costs were estimated with the use of VA data for 1-hour sessions, with 15 minutes of contact between the therapist and the patient for the robot-assisted therapy and 60 minutes for the intensive comparison therapy. We tracked patients' use of health care services and their costs using national VA databases. Patients reported any use of non-VA services or caregivers. Costs were standardized to 2008 dollars with the use of the general consumer price index. We analyzed costs, along with log-transformed costs.

Statistical Analysis

The trial was designed to test the superiority of robot-assisted therapy, as compared with intensive comparison therapy or usual care, with the use of a one-sided type I error of 0.025; however, two-sided P values are reported. The significance level was set at 0.022 (two-sided P value) to adjust for the two treatment comparisons and interim monitoring for the treatment effect.[11–16] The distributions of baseline characteristics were compared in the three groups by analysis-of-variance or chi-square tests, as appropriate, with a significance level of 0.05. Calculation of the sample size was based on the ability to detect a mean difference of 5 points in the Fugl-Meyer score between robot-assisted therapy and usual care and 3 points between robot-assisted therapy and intensive comparison therapy, on the assumption that the study would have a common standard deviation of 5 points, a loss-to-follow-up rate of 10%, and a power of 90%. The target sample size was 158 patients, with 26 assigned to usual care and 66 each to robot-assisted therapy and intensive comparison therapy. The rationale for selecting the effect sizes was based on a 3-point change in the Fugl-Meyer score, which represented a change that was clinically meaningful and of sufficient magnitude to differentiate patients on the basis of their disability score on the Modified Rankin Scale.[4] Because robot-assisted therapy was hypothesized to be much more effective than usual care, a 5-point difference was considered meaningful for this comparison.

We used sample variance to perform interim monitoring of maximum information for each study group for possible sample-size readjustment; treatment differences were monitored for efficacy and futility with the use of an information-based group sequential design with sloped boundaries.[11–16]

All analyses were performed according to randomized treatment assignment. Analysis of covariance was used to test the effect of treatment on the primary and secondary outcomes at

12 weeks, with adjustment for the study site as a fixed effect, the Comorbidity Disease Index, [17,18] and the baseline value of the outcome. For patients who missed the 12-week assessment, the next available post-treatment assessment was used, and patients who missed all post-treatment assessments were excluded from the 12-week analysis. Because randomization to usual care was stopped after 15 months as specified by the protocol, comparisons of robot-assisted therapy with usual care included only patients who were recruited during this period; comparisons between robot-assisted therapy and intensive comparison therapy included all patients who underwent randomization and were evaluated.

Secondary analyses used longitudinal methods to assess the effect of treatment on outcomes on the basis of all available data at 6, 12, 24, and 36 weeks. Sensitivity analyses were conducted with the use of multiple imputation to replace missing data. In addition, exploratory analyses were conducted to examine the association between outcomes and the time from the index stroke until study entry. Results are presented as least-squares means with standard errors or 95% confidence limits. All statistical analyses were performed with the use of SAS software, version 9.1.

RESULTS

Study Participation

From November 8, 2006, to October 31, 2008, we screened 200 patients, of whom 127 underwent randomization: 49 to robot-assisted therapy, 50 to intensive comparison therapy, and 28 to usual care (Fig. 1). Enrollment in the usual-care group was stopped after 15 months, when the target information had been attained per protocol. Recruitment to the robot-assisted and intensive-comparison groups continued until the scheduled end of enrollment at 24 months. The data and safety monitoring board did not recommend extending recruitment for these two treatment groups because the increase in sample size that would be necessary to achieve maximum information (a total of 262 patients) was not feasible, and conditional power to detect a treatment difference for the observed trend was low (2%).

The most common reason for exclusion of patients from the study was a baseline Fugl-Meyer score outside the required range of 7 to 38 points (see Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). A total of 111 patients (87%) completed the final study visit. The mean (±SD) number of therapy sessions attended was 33±8 for robot-assisted therapy and 32±8 for intensive comparison therapy, with a median of 36 sessions attended in both groups.

Baseline Characteristics of the Patients

The baseline characteristics of the treatment groups were similar, except for the time from the index stroke to randomization (P = 0.04 for all comparisons) (Table 1). The mean age was 64.6±11.3 years; 96% of the patients were men; 78% were white and 19% were black. The most frequent type of stroke was ischemic (in 85% of the patients). The average time from the index stroke until study entry was 4.7 years (range, 0.5 to 23.6), and 33% of the patients had multiple strokes that were identified on imaging. At baseline, the mean Fugl-

Meyer score was 18.9±9.5, the mean time on the Wolf Motor Function Test was 71.1±33.2 seconds, and the mean Stroke Impact Scale score was 49.4±14.7.

A total of 93 patients (73%) were receiving some form of rehabilitation therapy at baseline, and 30 patients (24%) were receiving therapy that targeted upper-limb function. The number of patients who were receiving nonstudy rehabilitation therapy was generally maintained over the follow-up period, with 84 patients (66%) receiving some type of rehabilitation therapy at 12 weeks and 86 patients (68%) at 36 weeks. The number of patients who were receiving therapy that targeted upper-limb function decreased slightly over time, with 20 patients (16%) receiving such therapy at 12 weeks and 17 (13%) at 36 weeks. There were no significant differences in the number of patients receiving nonstudy therapy across treatment groups at any time point.

Effectiveness

Primary Outcome—At 12 weeks, the mean Fugl-Meyer score for patients receiving robot-assisted therapy was better than that for patients receiving usual care (difference, 2.17 points; 95% confidence interval [CI], −0.23 to 4.58) and worse than that for patients receiving intensive comparison therapy (difference, −0.14 points; 95% CI, −2.94 to 2.65). However, the between-group differences were not significant (Table 2).

Secondary Outcomes—Patients receiving robot-assisted therapy, as compared with those receiving usual care, had significant improvement in motor function and social participation at 12 weeks, as measured on the Stroke Impact Scale, but there was no significant between-group difference in the speed of motor-task performance, as measured on the Wolf Motor Function Test.

The results of longitudinal analyses during the 36-week study period are presented in Figure 2. Patients receiving robot-assisted therapy had significantly more improvement in Fugl-Meyer scores and Wolf Motor Function Test times during the 36-week study period than did those receiving usual care. Differences between robot-assisted therapy and intensive comparison therapy were not significant. The results were similar when missing values were replaced by multiple imputation (data not shown). A longer interval between the index stroke and enrollment in the study was significantly associated with a worse Fugl-Meyer score at each time point and with worse scores on the Stroke Impact Scale over the 36-week study period. However, when the interval between the index stroke and enrollment was included in the adjusted models, the treatment effects were similar, and the conclusions did not change for any of the outcomes at any of the time points (data not shown).

Safety

There were no treatment-related serious adverse events (Table 3). Treatment-related adverse events were mild (e.g., transient muscle soreness); 12 patients (24%) receiving robot-assisted therapy and 9 (18%) receiving intensive comparison therapy reported having a nonserious treatment-related event. There were no significant differences in scores on numerical rating scales for pain or spasticity among treatment groups at 12 weeks or over a period of 36 weeks.

Cost Analysis

The average per-patient cost of therapy was $9,977 for patients receiving robot-assisted therapy and $8,269 for those receiving intensive comparison therapy. After 36 weeks, the average total cost (therapy plus the cost of all other health care use) was $15,562 for robot-assisted therapy, $15,605 for intensive comparison therapy, and $14,343 for usual care. The treatment differences were not significant on the basis of non–log-transformed costs, though the costs for the two active-therapy groups were significantly more than the cost for usual care on the basis of log-transformed cost models ($P<0.01$ for both comparisons).

DISCUSSION

In this study of rehabilitation strategies for patients with moderate-to-severe upper-limb impairment 6 months or more after a stroke, we found no significant benefit of robot-assisted therapy over intensive comparison therapy or usual care. At 12 weeks, there was no significant difference in primary or secondary outcomes, except for the score on the Stroke Impact Scale, which showed significant improvement with robot-assisted therapy, as compared with usual care. In secondary analyses, robot-assisted therapy had a significant but modest effect in improving motor function and motor recovery during the 36-week study period, as compared with usual care; similar improvements in these measures were also observed for intensive comparison therapy. Treatment methods and the duration of treatment appeared to be acceptable to patients, with approximately 90% of therapy sessions completed, on average. Adverse events were mild, and there were no reports of treatment-related serious adverse events.

Unlike most previous studies of rehabilitation strategies, which evaluated therapies in patients with less impairment after a single stroke and focused on the acute and subacute periods after the stroke,[19–29] our study used eligibility criteria that were broad, a factor that enhances the generalizability of our findings to an increased population of stroke survivors. As compared with patients in previous studies, our patients had more severe impairment for a longer period of time after their stroke, and approximately one third had had multiple strokes. These factors may have contributed to our finding that robot-assisted therapy at 12 weeks did not provide a benefit with respect to the primary outcome.

Rehabilitation studies that have been conducted during the acute stroke phase suggest that a change of 6 to 7 points (or 10%) in the Fugl-Meyer score is clinically meaningful because it advances the patient to the next stage of motor recovery.[30,31] However, the magnitude of change in the Fugl-Meyer score that is necessary to produce real-world effects for patients during long-term recovery may be smaller, especially for those with severe impairment. The improvements that were detected over a period of 36 weeks in our study provide evidence of potential long-term benefits of rehabilitation and challenge the widely held clinical belief that gains in motor function are not possible for long-term stroke survivors.[30] Moreover, the gains made by patients in the two active-treatment groups that were apparent during the 36-week study period may have occurred as incremental motor improvement was incorporated into the patient’s daily routine.

There is no universally accepted protocol for upper-limb rehabilitation after stroke, and treatment programs vary in the duration, intensity, and frequency of rehabilitative therapy. A major advantage of this study was that the protocols for active therapy controlled the intensity, duration, and method of movements to improve consistency and reproducibility of training. Both treatment protocols included a large number of sessions (36) and a large number of movements per session (more than 1000 vs. 45 for typical stroke treatment).[32] The modest levels of improvement that were observed in the two active-therapy groups during the 36-week study period suggest that high-intensity, repetitive, task-oriented movement training may be necessary for motor recovery. It is not known whether a shorter duration of therapy or fewer movements per session could have a similar effect because the robot-assisted training was delivered in a progression of four modules over the 12-week treatment period.

Limitations of the study include a preponderance of men (98%) and the lack of blinding in study-group assignments. In addition, at baseline, nearly one quarter of the patients were engaged in some form of rehabilitative therapy that targeted upper-limb function, and nearly one fifth reported receiving physical or occupational therapy. This high level of baseline rehabilitation was unexpected and may be partially explained by the self-selection of highly motivated patients or by increased access to rehabilitative services within the VA, as compared with the private sector. The average duration of upper-limb rehabilitation sessions at baseline was 3 hours per week, which was the same amount of time as the active therapies, thereby potentially affecting the power to detect treatment effects. Of note, the average time from the index stroke to randomization was approximately 2 years longer in the usual-care group than in the two active-therapy groups; however, the results were similar when the analyses were adjusted for this difference, and none of the conclusions changed. The proportion of patients who were engaged in rehabilitative therapy was generally maintained over the course of the study, and although there was a slight decrease in the number of patients receiving therapy that targeted upper-limb function over time, there were no significant differences across treatment groups at any time point.

In conclusion, we found that 36 1-hour, high-intensity sessions of robot-assisted rehabilitative therapy for stroke survivors who had had moderate-to-severe upper-limb impairment for at least 6 months did not significantly improve motor function, as compared with usual care or intensive comparison therapy, at 12 weeks. However, over the 36-week study period, robot-assisted therapy resulted in significant but modest improvements in motor capability and motor-task performance, as compared with usual care but not with intensive comparison therapy. The study provides evidence of the potential long-term benefits of intensive rehabilitation in patients with moderate-to-severe impairment even years after a stroke.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Appendix

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References

1. Lloyd-Jones D, Adams RJ, Brown TM, et al. Heart disease and stroke statistics — 2010 update: a report from the American Heart Association. Circulation. 2010; 121(7):e46–e215. [PubMed: 20019324]
2. Broeks JG, Lankhorst GJ, Rumping K, Prevo AJ. The long-term outcome of arm function after stroke: results of a follow-up study. Disabil Rehabil. 1999; 21:357–64. [PubMed: 10503976]
3. Krebs HI, Hogan N, Aisen ML, Volpe BT. Robot-aided neurorehabilitation. IEEE Trans Rehabil Eng. 1998; 6:75–87. [PubMed: 9535526]
4. Lo AC, Guarino P, Krebs HI, et al. Multicenter randomized trial of robot-assisted rehabilitation for chronic stroke: methods and entry characteristics for VA ROBOTICS. Neurorehabil Neural Repair. 2009; 23:775–83. [PubMed: 19541917]
5. Fugl-Meyer AR, Jääskö L, Leyman I, Olsson S, Steglind S. The post-stroke hemiplegic patient. 1. A method for evaluation of physical performance. Scand J Rehabil Med. 1975; 7:13–31. [PubMed: 1135616]
6. Volpe BT, Lynch D, Rykman-Berland A, et al. Intensive sensorimotor arm training mediated by therapist or robot improves hemiparesis in patients with chronic stroke. Neurorehabil Neural Repair. 2008; 22:305–10. [PubMed: 18184932]
7. Taub E, Miller NE, Novack TA, et al. Technique to improve chronic motor deficit after stroke. Arch Phys Med Rehabil. 1993; 74:347–54. [PubMed: 8466415]
8. Wolf SL, Lecraw DE, Barton LA, Jann BB. Forced use of hemiplegic upper extremities to reverse the effect of learned nonuse among chronic stroke and head-injured patients. Exp Neurol. 1989; 104:125–32. [PubMed: 2707361]
9. Duncan PW, Bode RK, Min Lai S, Perera S. Rasch analysis of a new stroke-specific outcome scale: the Stroke Impact Scale. Arch Phys Med Rehabil. 2003; 84:950–63. [PubMed: 12881816]
10. Bohannon RW, Smith MB. Interrater reliability of a modified Ashworth scale of muscle spasticity. Phys Ther. 1987; 67:206–7. [PubMed: 3809245]
11. Jennison C, Turnbull BW. Group sequential analysis incorporating covariate information. J Am Stat Assoc. 1997; 92:1330–41.
12. Idem. Group sequential methods with applications to clinical trials. Boca Raton, FL: Chapman & Hall/CRC; 2000.
13. Lan KKG, DeMets DL. Discrete sequential boundaries for clinical trials. Biometrika. 1983; 70:659–63.
14. Lan KK, Zucker DM. Sequential monitoring of clinical trials: the role of information and Brownian motion. Stat Med. 1993; 12:753–65. [PubMed: 8516592]
15. Mehta C, Tsiatis A. Flexible sample size considerations using information-based interim monitoring. Drug Inf J. 2001; 35:1095–112.
16. Scharfstein DO, Tsiatis AA, Robins JM. Semiparametric efficiency and its implication on the design and analysis of group-sequential studies. J Am Stat Assoc. 1997; 92:1342–50.

17. Rigler SK, Studenski S, Wallace D, Reker DM, Duncan PW. Co-morbidity adjustment for functional outcomes in community-dwelling older adults. Clin Rehabil. 2002; 16:420–8. [PubMed: 12061477]
18. Studenski SA, Lai SM, Duncan PW, Rigler SK. The impact of self-reported cumulative comorbidity on stroke recovery. Age Ageing. 2004; 33:195–8. [PubMed: 14960439]
19. Atteya AA. Effects of modified constraint induced therapy on upper limb function in subacute stroke patients. Neurosciences. 2004; 9:24–9. [PubMed: 23377299]
20. Dromerick AW, Edwards DF, Hahn M. Does the application of constraint-induced movement therapy during acute rehabilitation reduce arm impairment after ischemic stroke? Stroke. 2000; 31:2984–8. [PubMed: 11108760]
21. Dromerick AW, Lang CE, Birkenmeier RL, et al. Very Early Constraint-Induced Movement during Stroke Rehabilitation (VECTORS): a single-center RCT. Neurology. 2009; 73:195–201. [PubMed: 19458319]
22. Fasoli SE, Krebs HI, Stein J, Frontera WR, Hogan N. Effects of robotic therapy on motor impairment and recovery in chronic stroke. Arch Phys Med Rehabil. 2003; 84:477–82. [PubMed: 12690583]
23. Ferraro M, Palazzolo JJ, Krol J, Krebs HI, Hogan N, Volpe BT. Robot-aided sensorimotor arm training improves outcome in patients with chronic stroke. Neurology. 2003; 61:1604–7. [PubMed: 14663051]
24. Lum PS, Burgar CG, Shor PC, Majmundar M, Van der Loos M. Robot-assisted movement training compared with conventional therapy techniques for the rehabilitation of upper-limb motor function after stroke. Arch Phys Med Rehabil. 2002; 83:952–9. [PubMed: 12098155]
25. Page SJ, Levine P, Leonard A, Szaflarski JP, Kissela BM. Modified constraint-induced therapy in chronic stroke: results of a single-blinded randomized controlled trial. Phys Ther. 2008; 88:333–40. [PubMed: 18174447]
26. Page SJ, Sisto S, Levine P, McGrath RE. Efficacy of modified constraint-induced movement therapy in chronic stroke: a single-blinded randomized controlled trial. Arch Phys Med Rehabil. 2004; 85:14–8. [PubMed: 14970962]
27. Suputtitada A, Suwanwela NC, Tumvitee S. Effectiveness of constraint-induced movement therapy in chronic stroke patients. J Med Assoc Thai. 2004; 87:1482–90. [PubMed: 15822545]
28. van der Lee JH, Wagenaar RC, Lankhorst GJ, Vogelaar TW, Devillé WL, Bouter LM. Forced use of the upper extremity in chronic stroke patients: results from a single-blind randomized clinical trial. Stroke. 1999; 30:2369–75. [PubMed: 10548673]
29. Wolf SL, Winstein CJ, Miller JP, et al. Effect of constraint-induced movement therapy on upper extremity function 3 to 9 months after stroke: the EXCITE randomized clinical trial. JAMA. 2006; 296:2095–104. [PubMed: 17077374]
30. Jørgensen HS, Nakayama H, Raaschou HO, Vive-Larsen J, Støier M, Olsen TS. Outcome time course of recovery in stroke. II. Time course of recovery: the Copenhagen Stroke Study. Arch Phys Med Rehabil. 1995; 76:406–12. [PubMed: 7741609]
31. Feys HM, De Weerdt WJ, Selz BE, et al. Effect of a therapeutic intervention for the hemiplegic upper limb in the acute phase after stroke: a single-blind, randomized, controlled multicenter trial. Stroke. 1998; 29:785–92. [PubMed: 9550512]
32. Lang CE, Macdonald JR, Reisman DS, et al. Observation of amounts of movement practice provided during stroke rehabilitation. Arch Phys Med Rehabil. 2009; 90:1692–8. [PubMed: 19801058]

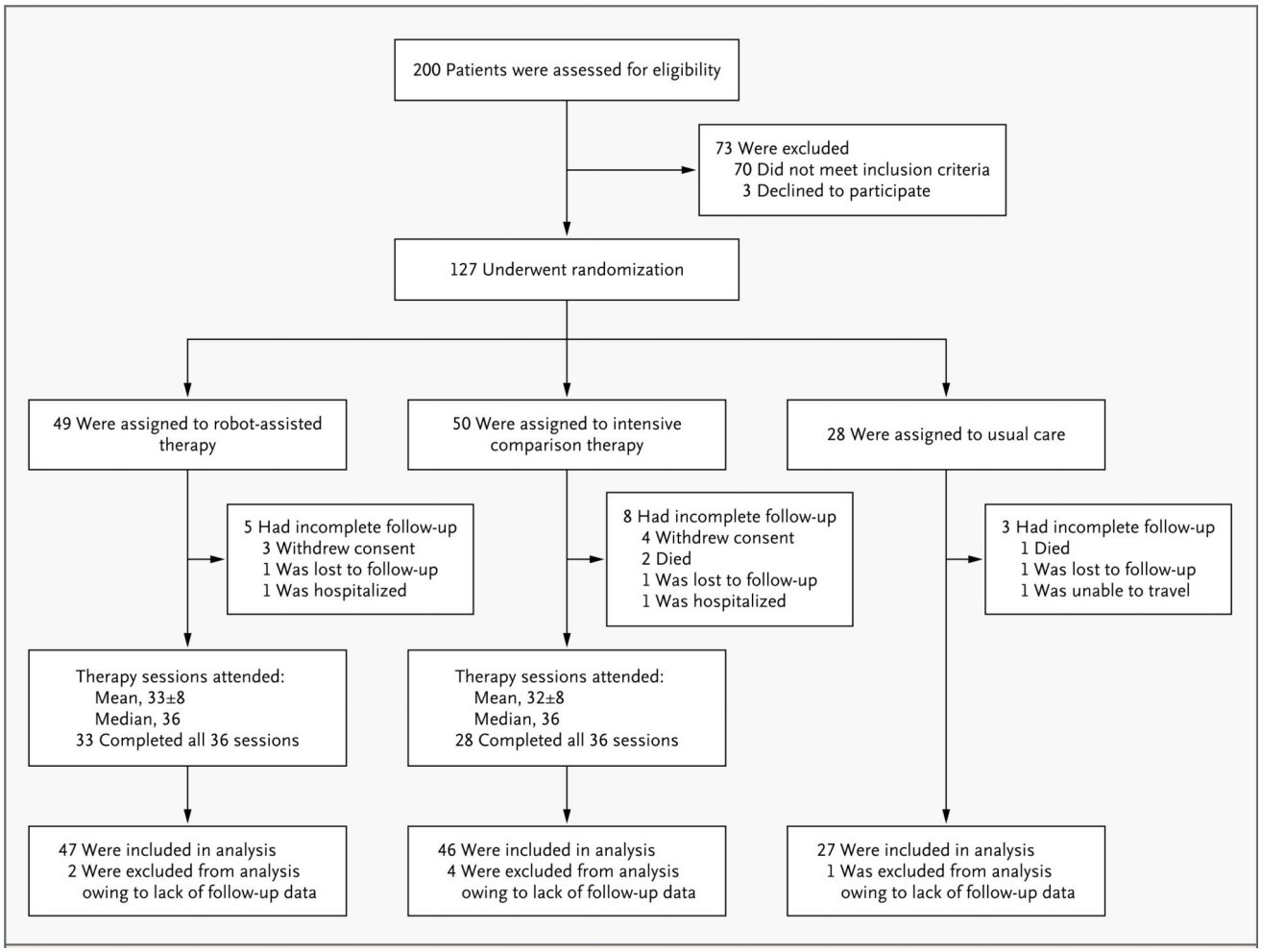

Figure 1.
Enrollment and Outcomes.

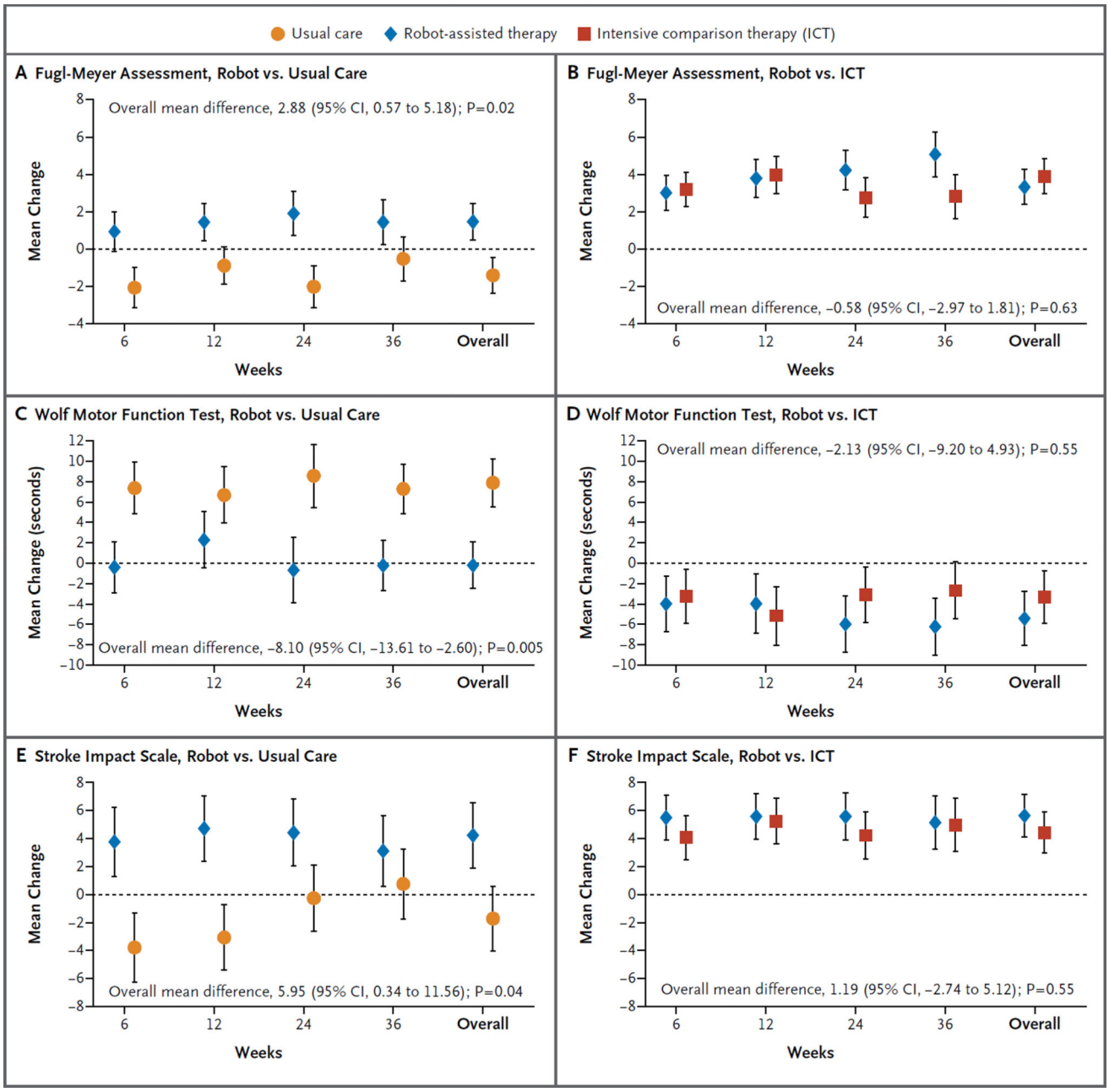

Figure 2. Changes in Primary and Secondary Outcomes during the 36-Week Study Period, as Compared with Baseline

Data are least-squares means at each time point and overall. Values have been adjusted for baseline scores, the Comorbidity Disease Index, and the study site as a fixed effect. For between-group comparisons of scores on the Fugl-Meyer Assessment (Panels A and B) and the Stroke Impact Scale (Panels E and F), higher scores indicate better functioning. For comparisons of scores (time) on the Wolf Motor Function Test (Panels C and D), higher scores indicate worse function. During the 36-week period, patients receiving robot-assisted therapy had significantly better performance than those receiving usual care on the Fugl-Meyer Assessment and the Wolf Motor Function Test, but the between-group difference on

the Stroke Impact Scale was not significant (P>0.022). Differences between patients receiving robot-assisted therapy and those receiving intensive comparison therapy (ICT) were not significant for any of the three tests. I bars indicate standard errors.

Table 1

Baseline Characteristics of the Patients.*

Characteristic	Robot-Assisted Therapy (N = 49)	Intensive Comparison Therapy (N = 50)	Usual Care (N = 28)
Age — yr			
Mean	66±11	64±11	63±12
Range	44–95	28–86	42–88
Sex— no. (%)			
Male	47 (96)	48 (96)	27 (96)
Female	2(4)	2(4)	1(4)
Race or ethnic group — no. (%)†			
White	39 (80)	37 (74)	23 (82)
Black	10 (20)	13 (26)	5(18)
Hispanic	1(2)	2(4)	0
Other	1(2)	2(4)	0
Index stroke type — no. (%)			
Hemorrhagic	7(14)	6(12)	6(21)
Ischemic	42 (86)	44 (88)	22 (79)
Index stroke location — no. (%)			
Anterior circulation			
≥1/3 of hemisphere	6(12)	14 (28)	6(21)
<1/3 of hemisphere	17 (35)	21 (42)	10 (36)
Small deep infarct	17(35)	15 (30)	6(21)
Posterior circulation	9(18)	0	6(21)
Time from index stroke to randomization — yr‡			
Mean	3.6±4.0	4.8±4.0	6.2±5.0
Range	0.6–19.8	0.5–15.7	0.5–23.6
Multiple strokes — no. (%)			
Self-reported with clinical history	11 (22)	10 (20)	5(18)
Identified on MRI or CT	18 (37)	17 (34)	7(25)

Characteristic	Robot-Assisted Therapy (N = 49)	Intensive Comparison Therapy (N = 50)	Usual Care (N = 28)
Medical history — no. (%)			
Musculoskeletal problem	16 (33)	12 (24)	13 (46)
Diabetes	14 (29)	13 (26)	9(32)
Mental health condition	13 (27)	12 (24)	10 (36)
Sleep disorder	9(18)	12 (24)	11 (39)
Glaucoma or cataract	16 (33)	10 (20)	4(14)
Myocardial infarction	9(18)	8(16)	8(29)
Congestive heart failure	9(18)	7(14)	6(21)
Cancer	8(16)	7(14)	5(18)
Peripheral vascular disease	5(10)	3(6)	5(18)
Chronic pain syndrome	3(6)	4(8)	6(21)
Angina	2(4)	3(6)	3(11)
Chronic obstructive pulmonary disease	3(6)	3(6)	1(4)
Comorbidity Disease Index— no. (%)[§]			
≤1 Domain	7(14)	7(14)	2(7)
2 Domains	13 (27)	24 (48)	8 (29)
≥3 Domains	29 (59)	19 (38)	18 (64)
Concomitant medication use — no. (%)			
Lipid-lowering agent	38 (78)	41 (82)	24 (86)
Aspirin or antiplatelet agent	42 (86)	41 (82)	19 (68)
Antihypertensive agent	41 (84)	39 (78)	21 (75)
Warfarin	14 (29)	13 (26)	7(25)
Antidepressant	19 (39)	15 (30)	14 (50)
Antianxiety agent	4(8)	9(18)	3(11)
Prescription pain drug	8(16)	10 (20)	6(21)
Baclofen	2(4)	6(12)	6(21)
Tizanidine	2(4)	2(4)	2(7)

Characteristic	Robot-Assisted Therapy (N = 49)	Intensive Comparison Therapy (N = 50)	Usual Care (N = 28)
Other muscle relaxant	4(8)	4(8)	4(14)
Other intervention — no. (%)			
Exercise (≥3 times/wk for 20 min)	19 (39)	22 (44)	14 (50)
Dietary management	15 (31)	14 (28)	10 (36)
Therapy targeting upper limb	12 (24)	9(18)	9(32)
Occupational therapy	7(14)	13 (26)	2(7)
Physical therapy	8(16)	7(14)	6(21)
Speech therapy	6(12)	5(10)	0
Smoking cessation	0	1(2)	2(7)
None	12 (24)	15 (30)	7(25)
Upper-limb therapy — hr/wk[¶]	2.6±1.8	4.0±3.7	3.6±4.2
Measurement of function			
Score on Fugl-Meyer Assessment[‖]	19.7±10.7	17.3±8.4	20.3±9.0
Wolf Motor Function Test[**]			
Score — sec	66.4±37.7	74.1±30.4	74.1±29.3
Tasks out of 15 performed within 120 sec — no.	7.9±5.0	8.8±4.0	8.9±3.8
Grip strength — lb	18.6±14.1	16.0±11.5	17.8±17.5
Score on Stroke Impact Scal[††]	49.2±14.8	50.5±15.1	48.1±14.2
Score on pain scale[‡‡]	1.2±2.1	1.7±2.3	1.5±1.8
Score on Modified Ashworth Scale[§§]	0.8±0.8	1.0±0.7	1.0±0.7

[*] Plus–minus values are means ±SD. To convert pounds to kilograms, divide by 2.2046. CT denotes computed tomography, and MRI magnetic resonance imaging.

[†] Race or ethnic group was self-reported, and patients could select more than one category.

[‡] P = 0.04 for all comparisons in this category. None of the other comparisons among study groups were significant.

[§] The Comorbidity Disease Index domains include cardiac, respiratory, neurologic, musculoskeletal, general (mental or emotional problems and sleep or pain disorders), cancer, diabetes, and visual problems. The domain scores are totaled to create an overall comorbidity score (≤1, 2, or ≥3 domains).

[¶] Time includes only that for therapy targeting upper limbs.

[‖] The Fugl-Meyer Assessment measures motor and sensory impairment in the upper limbs. The scale ranges from 0 to 66, with higher scores indicating better functioning.

** The Wolf Motor Function Test measures proximal and distal upper-limb motor control on 15 timed functional tasks, with an upper limit of 120 seconds per task. The tasks are averaged to produce a score that ranges from 0 to 120 seconds, with higher scores indicating worse functioning.

†† The Stroke Impact Scale is a self-reported measure of quality of life in the domains of hand function, activities or instrumental activities of daily living, mobility, and social participation. Scores range from 0 to 100, with higher scores indicating better functioning and greater social participation.

‡‡ The numerical rating scale for pain ranges from 0 to 10, with higher scores indicating worse pain.

§§ The Modified Ashworth Scale measures spasticity (muscle tone) on a scale of 0 to 5, with higher scores indicating more severe spasticity.

Table 2

Changes in Primary and Secondary Outcomes at 12 Weeks.*

Outcome	Robot-Assisted Therapy vs. Usual Care				Robot-Assisted Therapy vs. Intensive Comparison Therapy			
	Robot-Assisted Therapy (N = 25)	Usual Care (N = 27)	Mean Difference (95% CI)	P Value†	Robot-Assisted Therapy (N = 47)	Intensive Comparison Therapy (N = 46)	Mean Difference (95% CI)	P Value†
Change in score on Fugl-Meyer Assessment	1.11±1.01	−1.06±1.00	2.17 (−0.23 to 4.58)	0.08	3.87±1.05	4.01±1.06	−0.14 (−2.94 to 2.65)	0.92
Change in time on Wolf Motor Function Test‡	3.13±2.96	7.54±2.97	−4.41 (−11.52 to 2.70)	0.22	−3.96±3.00	−4.89±3.00	0.93 (−7.03 to 8.89)	0.82
Change in score on Stroke Impact Scale	4.61±2.36	−3.03±2.34	7.64 (2.03 to 13.24)	0.009	6.31±1.68	5.77±1.67	0.54 (−3.87 to 4.94)	0.81
Change in score on pain scale‡	−0.81±0.39	0±0.38	−0.81 (−1.73 to 0.11)	0.08	−0.61±0.29	0.24±0.30	−0.84 (−1.62 to−0.06)	0.03
Change in score on Modified Ashworth Scale‡	−0.03±0.11	−0.04±0.11	0.01 (−0.25 to 0.26)	0.95	−0.07±0.09	0.12±0.09	−0.19 (−0.42 to 0.04)	0.10

*Plus-minus values are means +SE. Patients receiving usual care were enrolled in the study for 16 months, and those receiving robot-assisted therapy were enrolled for 24 months. The analysis of robot-assisted therapy versus usual care included only patients receiving therapy during the same time period. The analysis of robot-assisted therapy versus intensive comparison therapy included all patients who underwent randomization and were evaluated. Values have been adjusted for baseline scores, the Comorbidity Disease Index score, and the medical center as a fixed effect. For patients who missed the 12-week assessment, the next post-treatment assessment, if available, was used.

†All P values are two-sided, with a significance level of 0.022 to adjust for the two treatment comparisons and interim monitoring for the treatment effect.

‡On this scale, a reduction in the score indicates improvement in the condition being evaluated.

Table 3

Adverse Events and Serious Adverse Events.*

Event	Robot-Assisted Therapy (N = 49)	Intensive Comparison Therapy (N = 50)	Usual Care (N = 28)
Adverse event			
Event related to study therapy— no. of patients (%)	12 (24)	9(18)	0
Type of event— no. of events			
Any	34	12	0
Pain, stiffness, or soreness	23	7	0
Fatigue	6	0	0
Swelling or bruising	1	3	0
Cut, scratch, or irritation	2	2	0
Numbness	2	0	0
Serious adverse event†			
Patients with event— no. (%)			
Any	11 (22)	18 (36)	9(32)
Death	0	2(4)	1(4)
Hospitalization	19 (39)	20 (40)	15 (54)
Other event reported by investigator	0	4(8)	0
Event related to study therapy — no. of events	0	0	0
Event unrelated to study therapy — no. of events			
Any	19	26	16
Cardiac disorder	1	3	3
Gastrointestinal disorder	0	3	0
General disorder	1	2	1
Hepatobiliary disorder	4	0	0
Infection or infestation	5	2	1
Injury, poisoning, or procedural complication	3	4	1
Neoplasm	0	2	0
Nervous system disorder	3	2	1

Event	Robot-Assisted Therapy (N = 49)	Intensive Comparison Therapy (N = 50)	Usual Care (N = 28)
Psychiatric disorder	0	1	1
Renal or urinary disorder	1	0	2
Respiratory, thoracic, or mediastinal disorder	0	1	1
Social circumstance‡	1	2	2
Surgical or medical procedure	0	2	2
Vascular disorder	0	2	1

*The principal investigator at each clinical site determined whether an adverse event or serious adverse event was related to a study therapy.

†Serious adverse events are listed according to the organ-classification system used in the *Medical Dictionary for Regulatory Activities*.

‡Social circumstance includes any social, lifestyle, or housing issues.