Efficacy of Upper Extremity Robotic Therapy in Subacute Poststroke Hemiplegia

An Exploratory Randomized Trial

Kayoko Takahashi, ScD, OTR; Kazuhisa Domen, MD, DMSc; Tomosaburo Sakamoto, MD, PhD; Masahiko Toshima, MD; Yohei Otaka, MD; Makiko Seto, MD, PhD; Katsumi Irie, MD, PhD; Bin Haga, MD, PhD; Takashi Takebayashi, OTR; Kenji Hachisuka, MD, DMSc

Background and Purpose—Our aim was to study the efficacy of robotic therapy as an adjuvant to standard therapy during poststroke rehabilitation.

Methods—Prospective, open, blinded end point, randomized, multicenter exploratory clinical trial in Japan of 60 individuals with mild to moderate hemiplegia 4 to 8 weeks post stroke randomized to receive standard therapy plus 40 minutes of either robotic or self-guided therapy for 6 weeks (7 days/week). Upper extremity impairment before and after intervention was measured using the Fugl–Meyer assessment, Wolf Motor Function Test, and Motor Activity Log.

Results—Robotic therapy significantly improved Fugl–Meyer assessment flexor synergy (2.1±2.7 versus −0.1±2.4; P<0.01) and proximal upper extremity (4.8±5.0 versus 1.9±5.5; P<0.05) compared with self-guided therapy. No significant changes in Wolf Motor Function Test or Motor Activity Log were observed. Robotic therapy also significantly improved Fugl–Meyer assessment proximal upper extremity among low-functioning patients (baseline Fugl–Meyer assessment score <30) and among patients with Wolf Motor Function Test ≥120 at baseline compared with self-guided therapy (P<0.05 for both).

Conclusions—Robotic therapy as an adjuvant to standard rehabilitation may improve upper extremity recovery in moderately impaired poststroke patients. Results of this exploratory study should be interpreted with caution.

Clinical Trial Registration—URL: http://www.umin.ac.jp/. Unique identifier: UMIN0000016199. (Stroke. 2016;47:1385-1388. DOI: 10.1161/STROKEAHA.115.012520.)

Key Words: hemiplegia ■ recovery ■ rehabilitation ■ robotics ■ stroke

Although stroke affects nearly 15 million people worldwide annually, with 5 million experiencing some degree of permanent paralysis,¹ appropriate rehabilitation programs can improve motor function and quality of life.² For example, repetitive voluntary movement of the paralyzed limb can improve function and remodel neural circuits.³ Robotic technologies may be effective for stroke rehabilitation because they can produce consistent repetitive patterns in an automated manner.⁴ However, although one recent systematic review reported that robot-assisted training improves activities of daily living and arm function,⁵ another reported that robotic therapy is not more effective than standard therapy, except as an adjuvant.⁶ The present study aimed to investigate whether robotic therapy is a more effective adjuvant to standard rehabilitation than self-guided therapy in subacute poststroke rehabilitation.

Materials and Methods

This prospective, multicenter, randomized, open, blinded end point, exploratory clinical trial examined robotic therapy combined with standard upper extremity (UE) therapy in patients with subacute poststroke hemiplegia. All study protocols were approved by the institutional review boards of each facility. Full study details are provided in the online-only Data Supplement.
Patients were recruited from inpatient stroke centers at 6 participating facilities. Eligible patients were 20 to 80-years-old, experienced their first stroke in the previous 4 to 8 weeks, and exhibited UE Brunnstrom stage III to IV movement. Full inclusion/exclusion criteria are included in the online-only Data Supplement. All participants provided written informed consent.

We a priori selected 30 patients per group, which in a post hoc power calculation gave 64.2% power to detect a 3-point difference in Fugl–Meyer assessment (FMA) scores, with 25-point variance between groups (P<0.05). Participants were randomized by central registration staff using Zelen’s method combined with the minimization method to control for confounders (age, sex, Oxfordshire Community Stroke Project classification, Brunnstrom stage, and facility).

All patients received 40 minutes of standard therapy and 40 minutes of either self-guided or robotic therapy daily for 6 weeks. Standard therapy, which was administered by an experienced therapist, depended on each patient’s condition and comprised UE exercises for stretching, range of motion, reaching, grasping/releasing, and pinching, as well as activities of daily living training. The robotic therapy system (ReoGo; Motorika Medical, Caesaria, Israel) included 5 preprogrammed movement patterns and 5 levels of robotic assistance targeted toward proximal upper limb function, which were selected by the therapist for each patient. Similarly, a therapist selected appropriate items and assistance levels from a list of self-guided exercises for self-guided therapy. In both groups, the patient performed the exercises alone with the therapist supervising from a distance for risk management and to ensure fidelity to the selected program. Participants in both groups were allowed to stop the session at any time if pain or fatigue was considered excessive.

Outcomes

Outcome measures were the FMA (UE section of the FMA [0–66 points] as well as the proximal UE [0–36 points] and flexor synergy [0–12 points] subscores), the Wolf Motor Function Test (WMFT; mean time [0–120 s] needed to perform each of 15 tasks and proximal UE tasks [7 tasks]), and the Motor Activity Log (amount of use and quality of movement for 14 activities of daily living on 6-point Likert scales [0–5 points]). We did not a priori select one primary effectiveness outcome. Each outcome was evaluated at baseline (before any rehabilitation) and after 6-week intervention by therapists blinded to the randomization.

Safety

Adverse events were defined as described in the online-only Data Supplement. Safety of the ReoGo system was also evaluated according to the occurrence of accidents during each session (eg, unexpected shutdown, overstretching of the arm), pain (measured by a 100-mm visual analogue scale), and muscle spasticity (measured using the modified Ashworth scale).

Statistical Analysis

Data were analyzed using SAS version 9.1.3 or JMP version 12.0.1 (SAS Institute, Cary, NC) and presented as the mean±standard deviation (SD). Baseline group differences were tested by Fisher exact test (categorical) or 2-sample t test (ordinal). Treatment effectiveness was evaluated by changes in FMA, WMFT, and Motor Activity Log (baseline versus postintervention) using 1- and 2-sample t tests (within- and between-group comparisons, respectively). Analysis of covariance was used to control for baseline FMA score.

For subgroup analyses, participants were divided into higher and lower UE function (FMA<30 and ≥30, respectively, where FMA=30 represented the baseline mean). Similarly, the WMFT score was categorized as ≥120 s or <120 s. McNemar and 2-sample Wilcoxon tests (within- and between-group comparisons, respectively) were conducted. P<0.05 was considered significant for all statistical comparisons. All statistical analyses were conducted by the first author who was blinded to treatment allocation.

Results

Study Participation

Of 715 patients screened between November 2008 and April 2010, 60 were randomized to either robotic or self-guided therapy in addition to standard rehabilitation (Figure). Four patients randomized to self-guided therapy did not complete the study. Baseline patient characteristics were not significantly different between groups (Table I in the online-only Data Supplement).

Effectiveness

Changes in FMA, WMFT, and Motor Activity Log scores from baseline to the end of the intervention period between the 2 groups are reported in Table. Change in total FMA UE score was not significantly different between groups (P=0.255). However, changes in FMA proximal UE and FMA flexor synergy were significantly different (P=0.048 and P=0.003, respectively). Although baseline FMA flexor synergy was significantly different between groups at baseline (6.7±3.9 versus 8.7±2.8, robotic versus self-guided, respectively; P=0.035), the change remained significant when baseline score was included as a covariate (difference, 1.4; 95% confidence interval, 0.15–2.60; P=0.028). No significant differences in total or proximal UE WMFT scores (P=0.764 and P=0.330, respectively) or in amount of use or quality of movement (P=0.982 and P=0.943, respectively) were observed. Results on other outcome measures (ie, Simple Test for Evaluating Hand Function [STEF], Range of Motion, Modified Ashworth Scale) are reported in Table II in the online-only Data Supplement.

The lower UE function class (FMA<30) exhibited a greater gain in FMA score under robotic therapy compared with self-guided therapy (6.6±5.1 versus 2.2±6.2; P=0.041). No significant difference in gain was observed in the higher UE function class (2.4±3.8 versus 1.7±4.9; P=0.764 and P=0.330, respectively). Although common poststroke adverse events were observed at comparable frequencies in each group, no serious adverse events related to the intervention were observed (Table IV in the online-only Data Supplement).

Safety

Although common poststroke adverse events were observed at comparable frequencies in each group, no serious adverse events related to the intervention were observed (Table IV in the online-only Data Supplement).

Discussion

A 9- to 10-point change in FMA UE has been reported as the minimal clinically important difference for UE motor recovery among patients with subacute stroke.7 In the present study, the greater gain in FMA because of robotic therapy compared with self-guided therapy (9.5 versus 6.9, respectively) amounted to a clinically significant improvement, which is consistent with other studies.5
Our subgroup analyses suggest that repetitive movement exercises, such as during robotic therapy, may benefit relatively severe acute/subacute poststroke patients who are beginning to naturally recover. Although some studies suggest that robotic therapy is not more effective than intensive therapist–guided therapy for improving UE function, our study used individualized rather than fixed robotic therapy programs, suggesting that individualized programs may promote successful intervention.

This study has several limitations: a focus on moderately impaired patients only; duration and intervention period not based on a pilot study; and no longitudinal follow-up. Future studies should investigate more severely impaired patients with long-term follow-up.

Conclusions
Our findings suggest that robotic therapy may be a useful alternative to self-training as an adjuvant to therapist-guided

### Table. Changes in Outcomes Between Robotic and Self-Guided Therapy Groups From Baseline to End of the Intervention Period

<table>
<thead>
<tr>
<th></th>
<th>Robotic Therapy (n=30)</th>
<th>Self-Guided Therapy (n=26)</th>
<th>Difference</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total FMA UE</td>
<td>9.5±7.9</td>
<td>6.9±8.8</td>
<td>2.6</td>
<td>−1.9 to 7.1</td>
<td>0.255</td>
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<tr>
<td>Proximal UE</td>
<td>4.8±5.0</td>
<td>1.9±5.5</td>
<td>2.8</td>
<td>0.0 to 5.7</td>
<td>0.048</td>
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<tr>
<td>Flexor synergy</td>
<td>2.1±2.7</td>
<td>−0.1±2.4</td>
<td>2.2</td>
<td>0.8 to 3.6</td>
<td>0.003</td>
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<tr>
<td>Total WMFT</td>
<td>−16.7±19.5</td>
<td>−18.5±24.7</td>
<td>1.8</td>
<td>−10.1 to 13.6</td>
<td>0.764</td>
</tr>
<tr>
<td>Proximal UE</td>
<td>−19.1±33.3</td>
<td>−9.8±37.6</td>
<td>−9.3</td>
<td>−28.3 to 9.7</td>
<td>0.330</td>
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<tr>
<td>MAL AOU</td>
<td>0.46±1.02</td>
<td>0.46±0.78</td>
<td>0.01</td>
<td>−0.49 to 0.50</td>
<td>0.982</td>
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<tr>
<td>MAL QOM</td>
<td>0.54±0.92</td>
<td>0.53±0.77</td>
<td>0.02</td>
<td>−0.44 to 0.48</td>
<td>0.943</td>
</tr>
</tbody>
</table>

Data are presented as mean±SD. AOU indicates amount of use; CI, confidence interval; FMA, Fugl–Meyer assessment; MAL, motor activity log; QOM, quality of movement; SD, standard deviation; UE, upper extremity; and WMFT, Wolf Motor Function Test.
standard rehabilitation, especially for some standard treatments, such as repetitive movement exercises, and in patients with more severe UE impairment. Results of this exploratory study should be interpreted with caution.

Sources of Funding
This work was supported by Teijin Pharma Ltd (Tokyo, Japan).

Disclosures
None.

References
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http://stroke.ahajournals.org/content/47/5/1385

Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2016/03/21/STROKEAHA.115.012520.DC1

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The efficacy of upper extremity robotic therapy in subacute post-stroke hemiplegia: an exploratory randomized trial

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¹Kitasato University, Kanagawa, Japan; ²Hyogo College of Medicine, Hyogo, Japan; ³Kansai Rehabilitation Hospital, Osaka, Japan; ⁴Tokeidai Memorial Hospital, Hokkaido, Japan; ⁵Tokyo Bay Rehabilitation Hospital, Chiba, Japan; ⁶Nagasaki Kita Hospital, Nagasaki, Japan; ⁷Hakujuji Hospital, Fukuoka, Japan; ⁸Kitakyushu Yahatahigashi Hospital, Fukuoka, Japan; ⁹The Hospital of Hyogo College of Medicine, Hyogo, Japan; ¹⁰Moji Medical Center, Fukuoka, Japan

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Supplemental Method:

Exploratory Clinical Study to Investigate the Efficacy, Safety, and Usefulness of Robotic System (ReoGo™) for Upper-limb Rehabilitation in Post-stroke Hemiplegia Patients

Protocol number: MER-11-001
Version number: Ver. 1.00
Draft date: September 1, 2008
## Protocol Synopsis

<table>
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<tr>
<th>Item</th>
<th>Description</th>
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<tr>
<td><strong>Study Title</strong></td>
<td>Exploratory Clinical Study to Investigate the Efficacy, Safety, and Usefulness of ReoGo Upper-limb Rehabilitation in Post-stroke Hemiplegia Patients</td>
</tr>
<tr>
<td><strong>Objective</strong></td>
<td>To investigate the efficacy, safety, and usefulness of the ReoGo system in recovery-phase rehabilitation of post-stroke hemiplegia patients by comparing training using ReoGo plus standard rehabilitation by an occupational therapist (OT) or physical therapist (PT), and therapist-directed self-training plus standard OT or PT rehabilitation.</td>
</tr>
<tr>
<td><strong>Study Design</strong></td>
<td>Prospective, randomized, multicenter, open-label, blind, parallel-group, comparative efficacy study</td>
</tr>
<tr>
<td><strong>Target Sample Size</strong></td>
<td>60 subjects</td>
</tr>
<tr>
<td><strong>Subjects</strong></td>
<td>Stroke patients with upper-limb hemiplegia</td>
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</tbody>
</table>
| **Inclusion Criteria** | 1. Clinically incipient stroke patients with upper-limb hemiplegia  
2. Patients expected to be hospitalized in a recovery-phase rehabilitation ward for the duration of the study  
3. Patients who experienced a stroke in the previous 4 to 8 weeks  
4. Upper-limb (shoulder/elbow) Brunnstrom stage III or IV at the time of providing informed consent  
5. Age between 20 and 80 years at the time of providing informed consent  |
<table>
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<tr>
<th>Exclusion Criteria</th>
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<tbody>
<tr>
<td>1. Brainstem stroke</td>
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<td>2. Vision disorders</td>
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<td>3. Hemorrhagic cerebral infarction (brain hemorrhage immediately after infarction) or subarachnoid hemorrhage</td>
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<td>4. Severe aphasia</td>
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<td>5. Inability to remain seated during training</td>
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<td>6. Intense pain in response to external pressure on affected upper limb</td>
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<td>7. Incapable of voluntary consent</td>
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<tr>
<td>8. Previous experience with robotic rehabilitation of upper-limb hemiplegia</td>
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<td>9. Previous experience with constraint-induced movement (CI) therapy of upper-limb hemiplegia</td>
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<tr>
<td>10. Previous experience with functional electrical stimulation (FES) therapy of upper-limb hemiplegia</td>
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<tr>
<td>11. Cardiac or respiratory disorders that may interfere with rehabilitation</td>
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<td>12. Other neuromuscular diseases</td>
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<td>13. Body weight of 110 kg or more</td>
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<tr>
<td>14. Other reasons deemed by the investigators or subinvestigators to render the subject unsuitable for treatment with the investigational device</td>
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<th>Discontinuation Criteria</th>
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<tr>
<td>1. Improvement in hemiplegic upper-limb function to the extent that continued training is no longer deemed necessary by the investigators or subinvestigators</td>
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<tr>
<td>2. Occurrence of adverse events that would make continued conduct of the study difficult</td>
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<td>3. Request by a subject to withdraw from the study</td>
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<td>4. Withdrawal of subject consent to participate in the study</td>
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<td>5. Serious or ongoing non-compliance with the protocol</td>
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<td>6. Other circumstances deemed by the investigators or subinvestigators to warrant discontinuation from the study</td>
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<tr>
<th>Intervention Methods</th>
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<tr>
<td>Treatment group: training with the ReoGo system (2 units) in addition to standard rehabilitation by a therapist (2 units)</td>
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<tr>
<td>Control group: therapist-directed self-training (2 units) in addition to standard rehabilitation by a therapist (2 units)</td>
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<tr>
<th>Intervention Period</th>
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<tr>
<td>6 weeks (daily)</td>
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<td>Endpoints</td>
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<tr>
<th>Observations/Tests</th>
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<tr>
<td>Study Schedule: see Table 1</td>
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<table>
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<tr>
<th>Prohibited Concomitant Therapy</th>
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<tr>
<td>1. Any other robotic rehabilitation of upper-limb hemiplegia</td>
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<tr>
<td>2. CI therapy</td>
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<tr>
<td>3. FES therapy</td>
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<td>4. Occupational or physical therapy of upper-limb hemiplegia exceeding 4 units/day (including clinical trials)</td>
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<th>Permitted Therapy</th>
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<tr>
<td>1. Patient self-training</td>
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<td>2. Therapy/training of areas of the body other than the hemiplegic upper limb</td>
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<td>3. Pharmacotherapy</td>
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| Study Duration | September 1,2008 - October 31,2009 |
| Study Sites | See Supplement 1 |
Table 1. Observation/evaluation endpoints & timing thereof

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<th>Timing</th>
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</table>

BS*: Brunnstrom Stage → evaluation of discontinuation criteria BS VI to take into account Ueda et al.’s 12-stage global evaluation of hemiplegia grade (http://www.ncbi.nlm.nih.gov/pubmed/7002829)

FM: Fugl-Meyer

STEF: Simple Test for Evaluating Hand Function

MI: Motricity Index

MAS: Modified Ashworth Scale

WMFT: Wolf Motor Function Test

ROM: Range of Motion

FIM: Functional Independence Measure

MAL: Motor Activity Log

VAS: Visual Analogue Scale
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1. Development History

1.1 Development history

Recent studies have demonstrated the effectiveness of active repetitive movements in recovery from brain injury\(^1\) and have reported that promoting active movement is effective in rebuilding damaged neural networks\(^2\).

The greatest appeal of robot technology in rehabilitation is that it enables automated, precise, repetitive movements, which makes robot rehabilitation devices an effective tool for therapists. When therapists perform patient rehabilitation, they begin with an initial evaluation in order to develop a suitable training program for restoring the motor function and capacity of the patient. Repeating this training with a robotic rehabilitation device can therefore realize a higher level of recovery. In fact, a previous study has reported the benefits of a robotic rehabilitation device on upper extremity motor function in stroke patients\(^3\).

ReoGo is a robotic rehabilitation device with a flexible joystick structure that was developed to provide effective upper-limb training in a three-dimensional (3D) environment. In addition to 3D motion, ReoGo features motion guidance, resistance force and speed settings that can be configured to provide upper extremity training approaching that of a therapist. Through integration with standard rehabilitation currently offered in Japan, the ReoGo system is expected to realize enhanced recovery of patient motor function and capacity.

ReoGo's mechanical and electrical safety and performance have been examined according to the Ministry of Health, Labour and Welfare (MHLW)'s certification standards for functional upper-limb passive motor training devices, and the system has already obtained medical device marketing approval in Japan. According to its marketing approval certificate, ReoGo is intended for use in the prevention of joint adhesion/contraction and improvement of range of movement (ROM), and is therefore indicated for a wide range of diseases requiring rehabilitation. In order to investigate the extent to which ReoGo enables recovery of motor function and capacity when used on stroke patients, we will conduct an exploratory study to determine the efficacy, safety, and usefulness of combining ReoGo with recovery-phase rehabilitation of stroke patients with hemiplegia.

1.2 Summary of previous significant clinical studies

A pilot study using ReoGo was conducted by Motorika in Berlin. Targeting 20 sub-acute stroke patients, this exploratory study examined the presence and magnitude of therapeutic effects of ReoGo training, with air splint therapy used as the control. The ReoGo group consisted of 11 patients and the control group contained 9 patients. Both the ReoGo group and control group exhibited significant improvements in the primary endpoints of upper-extremity Fugl-Meyer and Action Reach Arm Test (ARAT) test scores compared to baseline. Although the extent of post-intervention improvement in the ReoGo group was considerable, no significant difference was seen compared to the control group. Moreover, no serious adverse events (SAEs) were observed during the study.
2. Study Objective and Endpoints

2.1 Study objective
To investigate the efficacy, safety, and usefulness of the ReoGo system in recovery-phase rehabilitation of post-stroke hemiplegia patients by comparing training using ReoGo plus standard rehabilitation by an OT or PT, and OT- or PT-directed self-training plus standard OT or PT rehabilitation.

2.2 Endpoints
(1) Evaluation of hemiplegic upper limb impairment
   1. Change in Brunnstrom stage (BS) of shoulder/elbow recovery
   2. Change in upper extremity Fugl-Meyer (FM) score
   3. Change in Simple Test for Evaluating Hand Function (STEF) score
   4. Change in Motricity Index (MI) of shoulder joint flexion and elbow joint flexion
   5. Change in Modified Ashworth Scale (MAS) of elbow flexors, elbow extensors, forearm pronation, and forearm supination
   6. Change in 15 items of upper-extremity (shoulder/elbow) Wolf Motor Function Test (WFMT)
   7. Change in Range of Movement (ROM) of shoulder, elbow, forearm, and hand
(2) Evaluation of hemiplegic upper limb disability
   1. Change in Functional Independence Measure (FIM)
   2. Change in the 14 items of the Motor Activity Log (MAL) regarding amount of use (AOU) and quality of movement (QOM)
(3) Other evaluation
   1. Change in Visual Analog Scale (VAS) upper-limb pain assessment

Rationale:
BS, FM, and STEF were selected as efficacy endpoints of hemiplegic upper limb impairment because they are recognized in Japan as typical evaluation methods and because they enable comparison with findings from overseas clinical studies. MI was selected to evaluate muscle strength and MAS was selected to evaluate spasticity. Furthermore, WMFT was chosen to evaluate time-based measurements of upper limb impairment and ROM was chosen to evaluate the effects of training on upper limb mobility.

In addition, FIM and MAL were selected as efficacy endpoints of hemiplegic upper limb disability in order to examine the relationship between improvement in hemiplegic upper limb function and quality of life (QOL), and to assess activities of daily living (ADL) on the affected side respectively.
VAS was selected to investigate the pain-relieving effects of the investigational device.

(4) Safety endpoints
   ① AEs
   ② Intervention conditions
   ③ Physiological tests
Rationale:
Incidence of AEs was selected as the most objective endpoint for evaluating safety, while intervention conditions were selected to examine the effects of intervention. Physiological tests were also selected as a generally accepted means of confirming safety.

3. Study Design

3.1 Study design
This clinical trial is a prospective, randomized, multicenter, open-label, blind, parallel-group efficacy study comparing training using ReoGo plus rehabilitation by an OT or PT, and OT- or PT-directed self-training plus OT or PT rehabilitation in the recovery-phase rehabilitation of post-stroke hemiplegia patients. The duration of this study is 6 weeks.

Rationale:
A control group was established and a comparative study design was selected to evaluate the effects of robot-based recovery-phase rehabilitation. However, the comparison in this study of ReoGo robotic rehabilitation with self-training in addition to standard rehabilitation means that an open-label design had to be adopted to ensure uniform evaluation by blinding the evaluators. The study duration of 6 weeks was selected in consideration of the plateau phase typically observed in recovery-phase rehabilitation following a rise in the recovery curve.

3.2 Study duration
September 1, 2008 to October 31, 2009
(Subject participation period: October 1, 2008 to September 18, 2009)

3.3. Target sample size
30 subjects/group; total of 60 subjects

Rationale:
The target sample size was selected based on the number of patients deemed capable of being included within the duration of an exploratory clinical study.

4. Subjects

4.1 Target disease
Stroke patients with upper-limb hemiplegia

4.2 Inclusion criteria
Stroke patients who satisfy all of the following criteria (1)-(5) will be deemed eligible to enroll in the study by the investigators or subinvestigators.
(1) Clinically incipient stroke patients with upper-limb hemiplegia
(2) Patients expected to be hospitalized in a recovery-phase rehabilitation ward for the duration of the study
(3) Patients who experienced a stroke in the past 4 to 8 weeks
(4) Upper-limb (shoulder/elbow) Brunnstrom stage III or IV at the time of providing informed consent
(5) Aged between 20 and 80 years at the time of providing informed consent

**Rationale:**
(1) Determined based on the study objective.
(2) To target patients admitted for the purpose of undergoing post-stroke recovery-phase rehabilitation.
(3) Rehabilitative training is necessary to restore motor function in upper-limb hemiplegia patients, with recovery expected when this training is initiated within 4-8 weeks after stroke.
(4) Training is unlikely to restore motor function in BS I and II patients and there is little need for recovery-phase rehabilitation in BS V and VI patients.
(5) Patients aged 20-80 years are typically capable of providing consent and upper-limb hemiplegia patients in this age demographic can be expected to recover motor function through training.

### 4.3 Exclusion criteria

Stroke patients who meet any of the following criteria (1)-(14) will be deemed ineligible to enroll in the study by the investigators or subinvestigators.

(1) Brainstem stroke
(2) Vision disorders
(3) Hemorrhagic cerebral infarction (brain hemorrhage immediately after infarction) or subarachnoid hemorrhage
(4) Severe language comprehension disorders
(5) Inability to remain seated during training
(6) Intense pain in response to external pressure on affected upper limb
(7) Incapable of voluntary consent
(8) Previous experience with robotic rehabilitation of upper-limb hemiplegia
(9) Previous experience with CI therapy of upper-limb hemiplegia
(10) Previous experience with FES therapy of upper-limb hemiplegia
(11) Cardiac or respiratory disorders that may interfere with rehabilitation
(12) Other neuromuscular diseases
(13) Body weight $\geq 110$ kg
(14) Other patients deemed by the investigators or subinvestigators to be unsuited to treatment with the investigational device

**Rationale:**
(1) Brainstem stroke patients typically have serious impairment of motor function that is unlikely to be restored by training.
(2) ReoGo training requires the subject to look at a computer monitor.
(3) Recurrence of hemorrhagic cerebral infarction is likely to cause serious illness, while patients with subarachnoid hemorrhage exhibit different behaviors to those of other stroke
victims.
(4) Such subjects may not understand instructions from the physician or therapist.
(5) ReoGo training requires the subject to remain in a seated position.
(6) Training that causes pain to the subject would be difficult to perform.
(7) In consideration of the subject's human rights.
(8) - (10)
Patient bias such as carry-over effects or familiarity with the respective therapies would prevent proper evaluation of the efficacy, safety, and usefulness of ReoGo.
(11) Cardiac or respiratory disorders would make the training difficult to conduct.
(12) The effects of other neuromuscular diseases would prevent proper evaluation of the efficacy, safety, and usefulness of ReoGo.
(13) The seat used in the ReoGo training can only hold a load up to 110 kg.
(14) It is conceivable that the investigating physicians may decide that a subject is unsuitable to participate in the study due to scientific or ethical considerations other than those listed above.

4.4. Discontinuation criteria for individual subjects
If any of the following occurs after a subject has provided informed consent, the investigators or subinvestigators will discontinue the subject from the study and record the reason(s) for discontinuation in the Case Report Form (CRF). Refer to 12.2 Study discontinuation or suspension for details on the discontinuation/suspension of the entire study.
(1) Improvement in hemiplegic upper-limb function (BS VI) to the extent that continued training is no longer deemed necessary by the investigators or subinvestigators
(2) Occurrence of AEs that would make the continued conduct of the study difficult
(3) Request by a subject to withdraw from the study
(4) Withdrawal of subject consent to participate in the study (in this case, none of the subject's data will be used in evaluation/analysis)
(5) Serious or ongoing non-compliance with the protocol
(6) Other circumstances deemed by the investigators or subinvestigators to warrant discontinuation of the study

Rationale:
(1) Such an improvement would enable evaluation of efficacy before and after intervention and would eliminate the need to continue the study.
(2) In consideration of subject safety.
(3)-(4) In consideration of the subject's human rights.
(5) Non-compliance of this nature would make the subject ineligible for the study.
(6) Discontinuation of the study due to unforeseen circumstances may conceivably occur.
5. Informed Consent

5.1 Preparation of informed consent form and consent explanation form

(1) Before conducting the study, the investigators will cooperate with the clinical research director (CRD) to prepare the informed consent form (ICF), consent explanation form (CEF), and any other explanatory materials used to obtain the subject's consent to participate in the study.

(2) The prepared documents will be submitted to the CRD, who will then obtain the approval of the Institutional Review Board (IRB).

5.2 Timing, method & explanation of informed consent

(1) Timing & method of informed consent

1) After selecting subjects who are eligible for the study, the investigators or subinvestigators will use the CEF and other explanatory materials approved by the IRB to thoroughly explain the details and any other relevant matters of the study, and will then obtain the written consent of subjects to voluntarily participate in the study.

2) Before obtaining consent, the investigators or subinvestigators must provide subjects with the opportunity to ask questions and allow them sufficient time to decide whether to participate in the study. Furthermore, the investigators, subinvestigators, or other study collaborators providing additional explanation must respond to all questions in a manner that is satisfactory to the subject.

3) The ICF must be signed and dated by the explaining investigator or subinvestigator and the subject. If a study collaborator provided additional explanation, he/she must also sign and date the ICF.

4) The investigator or subinvestigator will then record the consent date in the CRF and submit a copy of the signed/dated ICF along with the CEF and other explanatory materials to the subject before participating in the study, with the investigator to archive the original at the study site.

5) The investigator or subinvestigator will confirm whether the subject has any other primary care physicians and, if so, must notify the physician of the subject's participation in the study after first obtaining consent from the subject.

(2) Details to be included on the CEF

1) What is a clinical study?

2) About your illness

3) About your current rehabilitation

4) Devices to be used in the study

5) Objective of the study

6) Methods to be used in the study

7) Estimated duration of your participation in this study

8) Rules for participating in the study

9) Estimated study population
Potential health risks of participating in this study
Your participation in this study is voluntary
You will be informed of any new material information about the study as it comes to light
You may withdraw from this study
We will access your medical records if you decide to participate in this study
Your privacy will be protected even if the results of this study are published
Medical costs of participating in this study
Remuneration for participating in this study
About the study physicians and consultation service
About the Institutional Review Board

5.3 Points to note on informed consent
The investigators or subinvestigators must obtain the subject's signed written consent to participate in the study. Consent must not be obtained from individuals who are deemed to be vulnerable.

The investigators, subinvestigators, and study collaborators must not use coercion or undue influence with regard to the subject's participation or continued participation in the study.
If the subject can understand the details of the CEF and other explanatory materials but is unable to sign the ICF due to paralysis etc., an explanation must be provided to both the subject and their legal representative using the CEF and other explanatory materials, after which the subject must provide verbal consent and the legal representative must sign the ICF before the subject and legal representative can be regarded as having understood the details of the study and as having consented to voluntarily participate in the study.

5.4 Amendments to the CEF
If the need to amend the CEF arises, it will be amended according to the following procedure.

(1) The investigators or subinvestigators will promptly inform the subject of any new material information that may affect the decision to continue participating in the study (e.g., additional safety information, changes to the protocol, etc.) and will record the details thereof along with the date in the relevant documents (such as the subject's original medical records) before amending the CEF. After notifying the subject of this new information, the investigators or subinvestigators must also confirm whether the subject is willing to continue participating in the study.
(2) If the investigators decide that the CEF must be amended, they will amend the CEF and other explanatory materials on the basis of the new information and obtain approval from the IRB.
(3) The investigators or subinvestigators will then repeat the explanation using the amended CEF and other explanatory materials, and will obtain voluntary written consent from the subject to continue participation in the study.
(4) The investigators or subinvestigators will then submit a copy of the new signed/dated ICF along with the CEF to the subject, with the investigator to archive the original at the study site.

6. Subject Enrollment

The investigators or subinvestigators will confirm that the subject satisfies all of the inclusion criteria and does not meet any of the exclusion criteria before obtaining consent. After consent has been obtained, the 'Subject Enrollment Form' (Attachment 2) will be filled out and faxed to the enrollment center and the enrollment procedure completed so that the study candidates can be assessed for eligibility and assigned to the treatment or control group. The investigators will then archive the original enrollment forms.

If the enrollment center confirms that the subject is eligible, it will assign the subject and notify the investigators and CRD of the results in the 'Notice of Enrollment Confirmation/Enrollment Number'. If, on the other hand, the enrollment center determines that the subject is ineligible due to a problem with eligibility, it will notify the investigators and CRD of this result in the 'Confirmation of Ineligibility' form without enrolling the subject.

The investigators or subinvestigators will then commence the study on subjects for whom a Notice of Enrollment Confirmation/Enrollment Number has been received, but will not conduct the study on subjects for whom a Confirmation of Ineligibility has been received. The study procedure up to the point of subject assignment is illustrated in Figure 1.

After the study is completed, the investigators will prepare the 'Subject Screening Log' (Attachment 1), assigning a subject identification code to each subject who was selected and provided consent, and then submit the log to the CRD. The Subject Screening Log will also contain the Subject Identification Code List and Subject Enrollment Log.

Enrollment center: Agrex Inc. (06-6310-9671)
Fax: 0120-176-702
Tel: 0120-176-701
Business hours: 8:00 a.m. - 6:00 p.m., Mon-Fri
(closed on weekends, public holidays and December 29 - January 4)
Fig. 1. Study procedure up to the point of subject assignment

Meets inclusion criteria & does not fulfill exclusion criteria

Obtain consent

Contact enrollment center

Decision on eligibility

Eligible

Assignment

Enrollment

ReoGo group

Standard rehabilitation of upper-limb hemiplegia
+ training with ReoGo

Control group

Standard rehabilitation of upper-limb hemiplegia
+ OT- or PT-directed self-training

Does not meet inclusion criteria or fulfills exclusion criteria

Cannot obtain consent

ICF

Archive

Cannot be enrolled

Confirmation of ineligibility

Submit to patient

CEF/ICF (copies)
7. Investigational Device

7.1 Investigational device name, etc.

The below-mentioned investigational device will be used in this study (see ReoGo package insert). The instructions for use, etc., are described in Supplement 4 'Instruction Manual for Medical Personnel' and Supplement 5 'Installation Guide for Medical Personnel'.

Table 2. Investigational device name, etc.

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Investigational device</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name</td>
<td>ReoGo</td>
</tr>
<tr>
<td>Manufacturer</td>
<td>Motorika (Israel)</td>
</tr>
<tr>
<td>Marketing approval no.</td>
<td>220ADBZX00083000</td>
</tr>
</tbody>
</table>

7.3 Investigational device handling

The CRD will prepare and distribute the 'Investigational Device Handling Procedure' to the study sites. Delivery, collection, storage, and handling of the device will be performed by the CRD and study sites in accordance with this procedure.

After concluding a clinical study agreement with the study sites, the CRD will deliver the device to the investigational device manager (IDM) at each site. Upon delivery, the IDM will accept a delivery note and sign a receipt after confirming the serial number and date.

Upon collection of the investigational device, the CRD will issue a collection form to the IDM, who will then sign a return form. The operating conditions of the investigational device and any failures will be recorded in each patient's CRF (see 8.2. Surveillance of intervention conditions).

7.4 Method of assigning subjects to treatment groups

In order to minimize any bias in subject demographics and ensure proper comparison of the ReoGo group and control group, subjects will be randomly assigned by the enrollment center following enrollment. The specific operations of the enrollment center are prescribed in the 'Subject Assignment Procedure'.

The assignment manager will prepare and archive the 'Subject Assignment Chart' securely until completion of the study.

7.5 Blinding method

This study aims to examine the effects of the ReoGo system on upper-limb hemiplegia by comparing results between a group using ReoGo with a group not using ReoGo, so it is not possible to maintain "blindness" among the subjects and the OTs or PTs observing the training. Evaluation of efficacy will therefore be undertaken by physicians who are not present during the training or by OTs or PTs participating in an instructional capacity, so blindness and objectivity will be maintained among these evaluators by withholding the details of subject assignment.
8. Methods & duration of intervention

8.1 Methods & duration of intervention

(1) Intervention methods/ intervention duration

Both the ReoGo group (i.e., treatment group) and control group will undergo 2 units (40 mins) of standard upper-limb hemiplegia rehabilitation by an OT or PT (Table 3. A). The treatment group will then undergo 2 units of ReoGo training based on Supplement 2 'Treatment Group Training Procedure' (Table 3. B), while the control group will perform 2 units of self-training under the direction of an OT or PT (Table 3. B). Training A and B will preferably be performed consecutively with as little interval as possible. The respective training units will also be conducted consecutively, but an interval may be provided according to the condition of the patient.

The date, intervention start/end time, presence or absence of interval and, in the case of the former, duration and reason for the interval will all be confirmed and recorded in the CRF.

Table 3. Intervention methods

<table>
<thead>
<tr>
<th></th>
<th>A. 2 units (40 min)</th>
<th>B. 2 units (40 min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ReoGo group</td>
<td>Standard upper-limb hemiplegia rehabilitation by OT or PT</td>
<td>Training with ReoGo</td>
</tr>
<tr>
<td>Control group</td>
<td>Standard upper-limb hemiplegia rehabilitation by OT or PT</td>
<td>OT- or PT-directed self-training</td>
</tr>
</tbody>
</table>

Rationale:

Two equal units of standard rehabilitation will be provided to both groups so as to ensure that all upper-limb hemiplegia patients participating in the study receive the necessary rehabilitation. Furthermore, 2 units of ReoGo robotic rehabilitation will be provided in the treatment group because this length of training is expected to be effective. The therapist-directed self-training in the control group is also set at 2 units, to match the intervention time with that of the treatment group.

(2) Intervention period

The intervention period will be 6 weeks of daily intervention.

Rationale:

Rehabilitative training is said to be significantly effective in the 3-month period following a stroke, so the intervention period of 6 weeks has been selected to allow the necessary and sufficient time to evaluate the training effects in consideration of the entry period of 4 to 8 weeks after stroke.

8.2 Surveillance of intervention conditions

The conditions of each intervention (start/end time, presence/absence of interval, and reason for interval) will be surveyed and recorded in the CRF. The conditions of any device failures (i.e., date, duration, nature of failure, measures taken, etc.) other than automatic stop due to overload detection will also be recorded in the CRF, along with the details of training or operations performed prior to the failure.
9. Treatment of subjects

9.1 Prior and concurrent therapy or medication

(1) Prohibited concomitant therapy
The following therapies are prohibited during the study period.
1. Any other robotic rehabilitation of upper-limb hemiplegia
2. CI therapy
3. FES therapy
4. Occupational or physical therapy of upper-limb hemiplegia exceeding 4 units/day (including clinical trials)

Rationale:
Each of these therapies would prevent proper evaluation of the efficacy, safety, and usefulness of ReoGo.

(2) Permitted therapies
The following therapies are permitted during the study period.
1. Patient self-training
2. Therapy on areas of the body other than the hemiplegic upper limb
3. Pharmacotherapy

Rationale:
These therapies should not be restricted for ethical reasons.

9.2 Subject compliance
The investigators or subinvestigators will explain the following compliance matters to the subjects before commencing the study.
(1) Do not use any robotic rehabilitation other than ReoGo during the study intervention period
(2) Do not reveal to the evaluating physician, OT or PT which group you belong to
(3) Follow the instructions of the investigators, subinvestigators, and occupational/physical therapists during the study period

Rationale:
(1) Use of other robotic rehabilitation devices would prevent proper evaluation of ReoGo's effects. (2) Compliance with this matter will ensure that the evaluation remains blind. (3) This is a common compliance matter for subjects participating in clinical studies.

9.3 Surveillance of concomitant medication & therapy
Details of all concomitant medications/therapies taken/undertaken during the study intervention period such as the reasons for use, route of administration (not required for therapies), daily dose (single dose for single-use drugs; not required for therapies), and start/end dates will be recorded in the CRF.
10. Observation/Evaluation Endpoints & Study Schedule

Table 10.1. Observation/evaluation endpoints & timing thereof

The observation/evaluation endpoints and the time point at which they will be conducted are shown in Table 4.

The investigators or subinvestigators will perform the predetermined evaluations within the stipulated acceptable interval.

Table 4. Observation/evaluation endpoints & timing thereof

<table>
<thead>
<tr>
<th>Timing</th>
<th>Informed consent</th>
<th>Enrollment</th>
<th>Baseline</th>
<th>3 weeks</th>
<th>End</th>
<th>Discontinuation date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acceptable interval</td>
<td>-7 days - enrollment</td>
<td>Informed consent - baseline</td>
<td>+ 1 days</td>
<td>+ 21 days ± 3 days</td>
<td>+ 42 days ± 3 days</td>
<td>Discontinuation date + 3 days</td>
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<tr>
<td>BS*</td>
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<td>ROM</td>
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<td>Intervention conditions</td>
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<tr>
<td>Physiological tests</td>
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<tr>
<td>Questionnaire survey</td>
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</tbody>
</table>

BS*: Brunnstrom Stage → evaluation of discontinuation criterion BS VI to take into account Ueda et al.'s 12-stage global evaluation of hemiplegia grade

FM: Fugl-Meyer
STEF: Simple Test for Evaluating Hand Function
MI: Motricity Index
MAS: Modified Ashworth Scale
WMFT: Wolf Motor Function Test
ROM: Range of Motion
FIM: Functional Independence Measure
MAL: Motor Activity Log
VAS: Visual Analogue Scale
10.2 Surveyed subject demographics

The investigators or subinvestigators will record the subject identification code, consent date, name of the person providing written consent, enrollment date, and enrollment number in the CRF. They will also conduct a survey of the following matters between the consent date and enrollment date, and record the results in the CRF.

1. Date of birth (Japanese calendar system acceptable)
2. Sex (male/female)
3. Body weight (to first decimal place)
4. Height (to first decimal place)
5. Handedness (left/right)
6. Disabled hand (left/hand)
7. Date of stroke (Gregorian calendar)
8. Type of stroke (cardioembolic; atherothrombotic; lacunar; other)
9. Oxford Community Stroke Project (OCSP) classification (LACI; TACI; PACI; POCI)
10. Brunnstrom stage III or IV (stages I, II, V or VI do not meet inclusion criteria)
11. Past medical history: name, date of onset, and date of recovery of any previous diseases recorded on the patient's recovery-phase rehabilitation ward medical record that required outpatient or inpatient care and that had resolved by the start of the investigational device intervention. This demographic also includes previous surgery.
12. Comorbidities: name, date of onset, and severity (see Table 5 'Severity criteria') of any diseases other than post-stroke upper-limb hemiplegia that the subject has at baseline.

10.3 Efficacy endpoints

The physicians, OTs, or PTs responsible for clinical evaluation will conduct the following evaluations (1)-(10) at the stipulated time.

1. Brunnstrom Stage (BS)
   BS will be evaluated for the shoulder and elbow only according to 6 stages (I-VI) based on Supplement 3 'Evaluation Manual'. Evaluation will be performed for each study intervention, and the evaluated BS will be recorded in the CRF along with the evaluation date. BS will also be evaluated upon discontinuation, and the evaluated BS will be recorded in the CRF along with the discontinuation date. In the event of a BS VI rating (which is a criterion for discontinuation), Ueda et al.'s 12-stage global evaluation of hemiplegia grade will also be considered in the evaluation (see Discontinuation Criteria on page 11).

2. Fugl-Meyer (FM)
   FM score will be determined in accordance with Supplement 3 'Evaluation Manual' for all affected-side upper extremity items (5 movements of shoulder, elbow, forearm, wrist, and hand; 7 finger movements; coordination and speed test), with a maximum score of 66 points. Evaluation will be performed at study commencement (baseline), Week 3, and study completion or discontinuation, and the respective scores will be recorded in the CRF along with the evaluation date.
(3) Simple Test for Evaluating Hand Function (STEF)

STEF will be evaluated in accordance with Supplement 3 'Evaluation Manual' by measuring the shortest possible time required for the subject to move objects specified in the 10 STEF subtests to a designated position. The respective time measurements will then be converted into scores, with the total score used for evaluation. Measurement times and scores will be recorded for both the left and right hands on a 'STEF-20P' form (Sakai Medical Co., Ltd.). Evaluation will be performed at baseline, Week 3, and study completion or discontinuation, and the left and right hand STEF scores will be recorded in the CRF along with the evaluation date.

(4) Motricity Index (MI)

Evaluation of MI will be performed based on Supplement 3 'Evaluation Manual' by assessing shoulder joint flexion and elbow joint flexion only according to the 6 manual muscle testing (MMT) grades (0-5) and converting them into MI scores, with the mean total score to be used for evaluation. Evaluation will be performed at baseline, Week 3, and study completion or discontinuation, and the MI score will be recorded in the CRF along with the evaluation date.

(5) Modified Ashworth Scale (MAS)

MAS will be evaluated for spasticity of elbow flexors, elbow extensors, forearm pronation, and forearm supination according to 6 grades (0, 1, 1+, 2, 3, and 4) based on Supplement 3 'Evaluation Manual'. Evaluation will be performed at baseline, Week 3, and study completion or discontinuation, and the MAS score will be recorded in the CRF along with the evaluation date.

(6) Wolf Motor Function Test (WMFT)

WMFT will be evaluated for all 15 tasks based on Supplement 3 'Evaluation Manual'. Subjects will be instructed to complete the tasks as quickly as possible, with the total required time to be used for evaluation. The task will be truncated if a subject takes more than 120 seconds to complete it. Evaluation will be performed at baseline, Week 3, and study completion or discontinuation, and the required task times (seconds) will be recorded in the CRF along with the evaluation date.

(7) Range of Motion (ROM)

ROM will be evaluated based on Supplement 3 'Evaluation Manual' by measuring the shoulder (8 measurements), elbow (2 measurements), forearm (2 measurements), and hand (2 measurements) to determine the respective ROM angles. Evaluation will be performed at baseline, Week 3, and study completion or discontinuation, and the respective ROM angles will be recorded in the CRF along with the evaluation date.
(8) Functional Independence Measure (FIM)

FIM will be evaluated based on Supplement 3 'Evaluation Manual' by rating the 13 physical items and 5 cognitive items on a scale of 1-7. Evaluation will be performed at baseline, Week 3, and study completion or discontinuation, and the respective scores will be recorded in the CRF along with the evaluation date.

(9) Motor Activity Log (MAL)

MAL will be evaluated based on Supplement 3 'Evaluation Manual' by asking the subject 14 questions about use of the paretic limb in activities of daily living (ADL) and assigning a score of 0-5 for each activity according to the amount of use (AOU) and quality of movement (QOM). Evaluation will be performed at baseline, Week 3, and study completion or discontinuation, and the respective scores will be recorded in the CRF along with the evaluation date.

(10) Visual Analogue Scale (VAS)

VAS will be evaluated by each subject based on Supplement 3 'Evaluation Manual' using a scale provided by the CRD (Fig. 2) by assigning a score between 0 and 100 to the most painful site of the affected upper extremity, with 100 representing the worst pain imaginable. Evaluation will be performed at baseline, Week 3, and study completion or discontinuation, and the VAS scores will be recorded in the CRF along with the evaluation date.

![Visual Analogue Scale (VAS)](image)

**Fig. 2 Visual Analogue Scale (VAS)**

**Rationale:**

(1) BS has been selected as an evaluation method because it focuses on synergic movement in the recovery process of hemiplegia patients with central nerve damage,
and is currently the most widely used test of motor function in post-stroke hemiplegia patients. BS will be evaluated for each intervention because it also corresponds to a discontinuation criterion (BS VI) based on improvement in motor function.

(2) FM has been selected because it is primarily a useful method for evaluating motor impairment in the rehabilitation phase, and is widely used in Europe to test motor function in post-stroke hemiplegia patients.

(3) STEF is a simple, objective, and quick way of determining upper extremity motor function (particularly speed of movement) that has been developed and standardized with the aim of evaluating therapeutic/training effects. It has been selected as an evaluation method in the present study because it provides a semi-quantitative result in the form of a score out of 100.

(4) MI is a useful method for evaluating improvement in muscle strength by measuring shoulder, elbow and finger joint flexion using manual muscle testing (MMT) and deriving an upper-limb MI score from the mean weighted score corresponding to the MMT. This study limits the ReoGo-based rehabilitation to the shoulder and elbow so MI will only be determined for shoulder and elbow joint flexion while finger joint flexion has been excluded.

(5) MAS has been selected because it is an internationally recognized spasticity scale that is also widely used in Japan to evaluate motor function impairment.

(6) WMFT has been adopted because it is a time-based quantitative method of evaluating impairment of upper extremity motor function.

(7) ROM has been selected as it is the most basic and significant method for evaluating restricted joint function caused by increased spasticity, rigidity, and pain resulting from central nervous system disorders.

(8) FIM has been selected because it is currently the world's most commonly used method for evaluating independence in ADL.

(9) MAL has been chosen because it is an important tool for evaluating the affected side of stroke patients based on an interview format assessing both AOM and QOM of the affected side in ADL.

(10) VAS has been adopted because it is an effective method for ascertaining the amount and change over time in pain, which is typically a difficult variable to evaluate.

10.4 Safety endpoints

(1) Adverse events

An adverse event (AE) is defined in this study as any clinically unfavorable or unintended disease, sign, symptom, clinical laboratory value (hematological, blood biochemistry and urine test values), or abnormal change in vital signs observed in a subject during the study intervention period.

Any event (disease, sign, or symptom) observed prior to the study intervention that has deteriorated after commencement of intervention compared to baseline will also be regarded as an AE.
If an AE is found to have occurred either by the subject's own admission or in the course of a medical examination, the investigators or subinvestigators will provide appropriate treatment and take all possible measures to minimize the risk to the subject's health.

(1) Assessment of AEs

The investigators or subinvestigators will record the following details of any AEs occurring during the study intervention period in the CRF: name of the AE (diagnosis where specified); date of onset (or date of medical exam on which symptom(s) were observed); greatest severity (mild, moderate, severe) and seriousness (serious/not serious); study intervention conditions (continued; suspended; discontinued); outcome (resolved, resolving, unchanged, worse, fatal, unknown); causal relationship with investigational device intervention (related/not related); and criteria for determining causal relationship (time of onset, primary disease, complication, concomitant medication/therapy, circumstances subsequent to study discontinuation, circumstances subsequent to study resumption, others).

AE severity will be determined according to the criteria in Table 5, causal relationship with investigational device intervention will be determined based on the criteria in Table 6, and AE outcome will be determined based on the criteria in Table 7.

AEs that meet the criteria specified in 11.1 Definition of serious adverse events will be regarded as serious AEs (SAEs) and will be handled according to the procedure described in 11.2 Handling of serious adverse events. Handling of subjects in the event of study discontinuation due to AEs, etc., will be performed according to 12.3 Discontinuation procedures.

Severity will be determined on the basis of the 'Classification of Serious Adverse Drug Reactions' (Notification No. 80 issued on 29 June 1992 by the Director of the Safety Division, Pharmaceutical Affairs Bureau, Ministry of Health and Welfare) and the criteria in Table 5 below.

<table>
<thead>
<tr>
<th>Class</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Mild</td>
<td>Patient can continue participating in the study without the need for treatment</td>
</tr>
<tr>
<td>2. Moderate</td>
<td>Patient requires treatment or study must be suspended (excluding treatment or suspension by decision of the patient)</td>
</tr>
<tr>
<td>3. Severe</td>
<td>Study must be discontinued and patient requires some form of treatment (excluding patient's decision to withdraw from the study)</td>
</tr>
</tbody>
</table>

Causal relationship of the AE with the investigational device intervention will be determined based on the reasonable likelihood of the following key factors.

1. Time of onset; 2. Primary disease; 3. Comorbidity; 4. Concomitant medication/therapy;
5. Circumstances subsequent to discontinuation of intervention; 6. Circumstances subsequent to resumption of intervention; and 7. Others

Table 6. Causal relationship criteria

<table>
<thead>
<tr>
<th>Classification</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Unrelated (causal relationship can be ruled out)</td>
<td>The causal relationship will be regarded as 'unrelated' if the temporal relationship between AE onset and investigational device intervention is unreasonable, or if there is a medically valid explanation for the cause of the AE other than the intervention.</td>
</tr>
<tr>
<td>2. Related (causal relationship cannot be ruled out)</td>
<td>The causal relationship will be regarded as 'related' if the AE does not satisfy criterion 1. above. AEs that are causally related to the investigational device intervention will be regarded as a device failure.</td>
</tr>
</tbody>
</table>

Table 7. Outcome criteria

<table>
<thead>
<tr>
<th>Class</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Resolved</td>
<td>Patient exhibits remission of symptoms or returns to pre-intervention condition</td>
</tr>
<tr>
<td>2. Resolved</td>
<td>Patient exhibits improvement in symptoms or laboratory values</td>
</tr>
<tr>
<td>3. Unchanged</td>
<td>No change in symptoms or laboratory values</td>
</tr>
<tr>
<td>4. Worse</td>
<td>Deterioration in symptoms or laboratory values</td>
</tr>
<tr>
<td>5. Fatal</td>
<td>Patient died due to AE</td>
</tr>
<tr>
<td>6. Unknown</td>
<td>Patient lost to follow-up</td>
</tr>
</tbody>
</table>

2) Follow-up of AEs

AEs that have not resolved by the end of the study intervention will be subject to post-study follow-up until the patient is discharged or transferred, and the results will be recorded in the CRF. AEs caused by investigational device failure will be subject to follow-up until they are resolved or resolving, and the results will be recorded in the CRF. If, for some reason, a follow-up is not conducted, the reason will be recorded in the CRF in column 5.9 'Comments'.

(2) Intervention conditions

The investigators or subinvestigators will record the start and end time of the study intervention in the CRF. The time and reason for any respite or suspension in the study intervention will also be recorded in the CRF.

Respite: any instance where the scheduled day's training was not performed or interrupted
Suspension: any instance where the scheduled day's training was temporarily halted and then
resumed within the allotted training time
Discontinuation: any instance where the patient's subsequent participation in the trial is canceled (in this instance, details of the discontinuation will be entered in the CRF's 'Study Termination/Discontinuation' column)

(3) Physiological tests
The investigators or subinvestigators will conduct the following physiological tests at the prescribed time.

Physiological tests: blood pressure; heart rate; body temperature (tests will be conducted in the morning in the patient's ward prior to commencing training)

10.5 Questionnaire survey
Evaluating the subjective usefulness and operability of the ReoGo system would prove difficult based solely on evaluation of efficacy and safety, so the 'ReoGo Questionnaire Survey' (Attachment 3) targeting the study's medical personnel and subjects will be conducted upon study completion or discontinuation. The survey results will be tabulated and analyzed independent of the efficacy and safety evaluations.

11. Ensuring subject safety
The investigators and subinvestigators will endeavor throughout the study period to collect and communicate safety information related to the study, and to maintain constant awareness of subject health through various measures such as ensuring contact with the subject in the event of an emergency.

The investigators or subinvestigators will also ensure the safety of the subjects in the event of an AE by providing appropriate treatment.

The CRD will stipulate appropriate procedures for each study site and confirm the safety of the subjects. The CRD will also confirm the existence of clinical laboratory data (i.e., hematological, blood biochemistry and urine test data) for each subject immediately after the start and end/discontinuation of the intervention

11.1 Definition of serious adverse events
The definition of serious adverse events (SAEs) according to this study is shown in Table 8.

<table>
<thead>
<tr>
<th>Table 8. Serious adverse events</th>
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<td>6</td>
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<td>7</td>
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</tbody>
</table>
11.2 Handling of serious adverse events

(1) Handling of subjects

1) SAEs

In the event of an SAE, the investigators or subinvestigators will ensure the safety of the patient by notifying them of the need for any medical care to treat the SAE and taking the necessary measures including appropriate provision of medical care.

2) Non-serious AEs

The investigators or subinvestigators will notify the subject of the need for any medical care to treat the AE and will then proceed to provide the appropriate treatment.

(2) Reporting to the study site director and CRD

1) SAEs

① Investigators will immediately report the occurrence of any SAEs, regardless of the causal relationship with the investigational device intervention, to the director of the study site and the CRD by fax etc. using Attachment 4 'Serious Adverse Events Report (Summary)'.

Contact:
Tel: Mobile:
Fax:

② Investigators will then promptly submit a detailed written report using Attachment 5 'Serious Adverse Events Report (Full Report)'.

③ Investigators will provide additional information when requested by the CRD, study site directors, or IRB.

④ After receiving notification of a serious, unforeseeable device failure from the CRD or an SAE from the site's investigator, the study site director will submit to a review by the IRB on the propriety of continuing the study at the study site.

2) Events requiring special consideration

The investigators or subinvestigators will immediately report the occurrence of an event requiring special consideration (i.e., serious device failures) to the CRD in a document containing details of the event along with the measures taken.

3) Non-serious AEs

In the event of a non-serious AE, the investigators or subinvestigators will report the event details to the CRD where appropriate.

11.3 Provision of new information

The CRD will immediately report any new material information relating to the safety of the study to the investigators and study site directors, and take the necessary measures.
11.4 Foreseeable failures

Muscular pain, pain, joint pain, and elevated blood pressure are all conceivable failures that may occur due to excessive training, but these will be avoided wherever possible by having subjects perform training under the instruction of an OT or PT, and appropriate measures will immediately be taken if any of these failures should occur.

No reports from overseas clinical studies have described failures caused by the ReoGo system.

12. Study Termination, Discontinuation or Suspension

12.1 Study termination

After the evaluations/observations prescribed in the protocol have been conducted on all subjects at the study site, the investigators will notify the site director of the study completion and submit a written summary of the study results.

The study site director will then notify the IRB and CRD in writing that the study has been completed, and submit a synopsis of the study results based on the investigators' summary.

12.2 Study discontinuation or suspension

If any of the following matters occur, the CRD will conduct a review on whether the study should be discontinued according to the protocol at all or some of the study sites.

1) Upon learning of matters concerning the quality, efficacy, and safety of the investigational device or any other information that is material to the proper conduct of the study

2) If changes to the protocol become necessary, but the study site is incapable of accommodating said changes

3) If the study site director instructs the CRD to make an protocol based on the advice of the IRB, but the CRD cannot consent to said amendment

4) If the IRB determines that the study should not be continued and the study site director issues an instruction to discontinue the study

5) If the study site commits a serious or ongoing violation of medical device good clinical practice (GCP), the protocol, or study agreement

If the CRD decides to discontinue or suspend the study, it will immediately notify the study site director of the decision and the reason(s) thereof in writing.

Upon receiving notification of the CRD's decision to discontinue or suspend the study, the study site director will immediately notify the investigator and the IRB of the decision and the detailed reason(s) thereof in writing.

Upon receiving the study site director's notification of the CRD's decision to discontinue or suspend the study, the investigator will immediately notify the subjects of the decision and ensure that the appropriate treatment and subsequent processing are performed.

Handling of individual subjects in the event of study discontinuation will be undertaken
12.3 Discontinuation procedures

If a subject is found to have fulfilled any of the discontinuation criteria (4.4. Discontinuation criteria for individual subjects) or if the study is suspended or discontinued, the investigators or subinvestigators will notify the subject to that effect, discontinue the study intervention, and contact the CRD.

The investigators or subinvestigators will conduct the relevant observations/evaluations upon discontinuation of the study, and provide the appropriate medical care and procedures after discontinuation of the study.

In the case of discontinuation of individual subjects, the discontinuation date (final observation date) and reason(s) for discontinuation will be recorded in the CRF. Details of surveillance/procedures carried out up to the time of discontinuation as well as the date of follow-up observations, method of confirmation, and condition following discontinuation will be recorded in the General Comments column of the CRF where necessary.

The investigators or subinvestigators will conduct the following procedures in response to the below-mentioned reasons for discontinuation.

1) Discontinuation due to safety concerns such as occurrence of an AE or exacerbation of comorbidity

The investigators or subinvestigators will perform appropriate treatment on discontinued subjects and conduct follow-up of AEs. If a subject is discontinued due to occurrence of an SAE, the investigators or subinvestigators will adhere to the procedures stipulated in 11 Ensuring Subject Safety.

2) If it becomes clear after commencement of the study that the subject cannot attend the study site

The investigators or subinvestigators will attempt to confirm the health and safety of the subject and the reason(s) for their non-attendance by telephone, and will record the details in the CRF.

3) Upon notification of study discontinuation from the CRD

The investigators or subinvestigators will promptly notify all subjects currently participating in the study of the discontinuation and will provide an alternative therapy or other appropriate treatment.

4) If the investigator discontinues or suspends the study due to doubts about the safety of the investigational device

The investigator shall immediately notify the study site director of the discontinuation/suspension in writing, and submit a detailed written explanation of the reason(s) thereof. The study site director will then immediately notify the IRB and CRD of the discontinuation/suspension in writing.
13. Statistical Analysis

The main statistical principles are described in the following sections, but the Statistical Analysis Plan (SAP) contains a more technical and detailed explanation of the analysis parameters and methods.

13.1 Analysis Sets

Primary efficacy analysis will be performed on the full analysis set (FAS), while secondary efficacy analysis will be done using the per protocol set (PPS). Safety analysis will be conducted on the safety analysis set (SAS).

Each of the analysis sets are defined below.

(1) Full analysis set (FAS)
All enrolled patients who undergo at least 1 study intervention and who are subject to post-intervention evaluation of efficacy

(2) Per protocol set (PPS)
All enrolled patients without any serious protocol violations as stipulated in the Patient Handling Criteria

(3) Safety analysis set (SAS)
All enrolled patients who undergo at least 1 study intervention and who are subject to post-intervention evaluation of safety

13.2 Demographic and other baseline characteristics

Distribution by group and descriptive statistics will be calculated for demographic and other baseline characteristics (patient demographics) and their comparability will be examined. Analysis of categorized data will be performed according to data characteristics using Fisher's exact test or the chi-square test, while sequential data will be analyzed using the Wilcoxon two-sample test and metric data will be analyzed using a two-sample t-test.

Bias in patient demographics will be determined using a two-sided significance level of 15%, and variables with a significance level below 15% will be evaluated where necessary to determine the effects of their bias on efficacy endpoints.

13.3 Efficacy analysis

(1) Brunnstrom Stage (BS)

① Change in baseline BS at the end of intervention will be subject to intergroup comparison using the Wilcoxon two-sample test and intragroup comparison using the single-sample Wilcoxon test.

② Time from baseline to adequate improvement (Stage VI) will be subject to survival analysis (Kaplan-Meier and log-rank test) and intergroup comparison of recovery time will also be performed.

(2) Fugl-Meyer (FM)

Change in baseline individual and total scores for 5 movements of shoulder, elbow, forearm, wrist, and hand, 7 finger movements, and coordination/speed test at study
completion will be subject to intergroup comparison using the Wilcoxon two-sample test and intragroup comparison using the single-sample Wilcoxon test. Analysis of covariance (ANCOVA) will also be performed using baseline values as the covariate, and the effect on outcome will be examined.

(3) Simple Test for Evaluating Hand Function (STEF)
Change in baseline left and right hand total scores obtained from time required to complete each subtest at study completion will be subject to intergroup comparison using the Wilcoxon two-sample test and intragroup comparison using the single-sample Wilcoxon test. ANCOVA will also be performed using baseline values as the covariate, and the effect on outcome will be examined.

(4) Motricity Index (MI)
Change in baseline shoulder and elbow joint flexion individual and mean total MI scores at study completion will be subject to intergroup comparison using the Wilcoxon two-sample test and intragroup comparison using the single-sample Wilcoxon test.

(5) Modified Ashworth Scale (MAS)
Change in baseline MAS grades for elbow flexors, elbow extensors, forearm pronation, and forearm supination at study completion will be subject to intergroup comparison using the Wilcoxon two-sample test and intragroup comparison using the single-sample Wilcoxon test.

(6) Wolf Motor Function Test (WMFT)
Change in baseline total time required to complete 15 tasks at study completion will be subject to intergroup comparison using the Wilcoxon two-sample test and intragroup comparison using the single-sample Wilcoxon test. ANCOVA will also be performed using baseline values as the covariate, and the effect on outcome will be examined.

If the time required to complete a single task exceeds 120 seconds, the time taken for that task will be recorded as 120 seconds.

(7) Range of Motion (ROM)
Change in baseline ROM angles of each variable at study completion will be subject to intergroup comparison using the Wilcoxon two-sample test and intragroup comparison using the single-sample Wilcoxon test. ANCOVA will also be performed using baseline values as the covariate, and the effect on outcome will be examined.

(8) Functional Independence Measure (FIM)
Change in baseline individual and total scores of 13 physical items and 5 cognitive items at study completion will be subject to intergroup comparison using the Wilcoxon two-sample test and intragroup comparison using the single-sample Wilcoxon test.

(9) Motor Activity Log (MAL)
Change in baseline mean AOU and QOM scores in response to 14 questions at study completion will be subject to intergroup comparison using the Wilcoxon two-sample test and intragroup comparison using the single-sample Wilcoxon test.

(10) Visual Analogue Scale (VAS)
Change in baseline VAS measurements at study completion will be subject to intergroup
comparison using the Wilcoxon two-sample test and intragroup comparison using the single-sample Wilcoxon test. ANCOVA will also be performed using baseline values as the covariate, and the effect on outcome will be examined.

13.4 Safety analysis

(1) Adverse Events

① AE incidence will be calculated for each group.
② Severity, seriousness, duration of onset, clinical study conditions, outcome, and causal relationship with investigational device will be tabulated for each group.

(2) Intervention conditions

① Descriptive statistics and performance rates at each study site will be calculated in the ReoGo group for the respective and total time spent on standard upper-limb hemiplegia rehabilitation by an OT and ReoGo-based self-exercise, and in the control group for the respective and total time spent on standard upper-limb hemiplegia rehabilitation by an OT and OT-directed self-exercise.
② Presence or absence of respite/suspension of intervention and reason thereof will be tabulated for each intervention method, group, and study site.

(3) Physiological tests

Descriptive statistics of blood pressure, heart rate, and body temperature will be determined for each group and time point. Descriptive statistics for change from baseline will also be calculated for each group and time point, and tested using a single-sample \( t \)-test.

13.5 Determination of sample size

Target sample size was set at 60 patients (30 patients/group).

Rationale:
The target sample size was selected based on the number of patients deemed capable of being included within the duration of an exploratory clinical study.

13.6 Other statistical analysis items

1) Handling of missing values and outliers

1. Missing values

Handling of missing values is described in the SAP, and will ultimately be determined at the data review meeting (DRM).

2. Outliers

While occurrence of outliers is not anticipated in the study planning stage, their effect on the analyses will be examined where necessary.

2) Data transformation

Data transformation will be conducted as appropriate if bias is seen in the data distribution.
3) Test significance level and confidence interval
   A two-tailed significance level of 5% and a two-sided confidence interval of 95% will be adopted for statistical tests. However, a two-tailed significance level of 15% will be used for analysis of intergroup homogeneity in demographic and other baseline characteristics.

(4) Multiple comparison/multiplicity
   This is an exploratory study, so no adjustment for multiplicity will be carried out.

(5) Adjustment for covariates
   Adjustment for covariates will be made where necessary.

(6) Interim analysis
   No interim analysis is planned.

(7) Others
   Additional exploratory analysis will be conducted where necessary.

14. Protocol Compliance, Deviations, Changes & Amendments

14.1 Protocol compliance
   The CRD will provide the investigators with the necessary materials and information to prepare the protocol, sample CRF, investigator's brochure (IB), and CEF.
   The investigators will discuss and review the ethical and scientific validity of conducting the study with the CRD based on the provided materials and information, and will conclude an agreement with the CRD on protocol compliance as well as the protocol itself and the sample CRF.
   The investigators and CRD will then attest to this agreement by signing and dating the protocol or an alternative document.

14.2 Protocol deviations or changes
   (1) The investigators and subinvestigators shall not deviate or modify the protocol without a prior written agreement with the CRD and written approval based on a prior review by the IRB except in the following circumstances.
      1) To prevent impending risks to the subjects or due to other compelling medical reasons
      2) Changes pertaining solely to clerical matters (e.g., changes to telephone numbers)
   In the case of 1) above, the investigators must submit in writing the details and reason(s) for the deviation or change as soon as possible for approval by the CRD, study site director and IRB, and must obtain the written agreement of the study site director and the CRD.
   (2) The investigators and subinvestigators shall record all actions that deviate from the protocol and submit a 'Record of Protocol Deviations' explaining the reason(s) thereof to the CRD while retaining a copy.
   (3) The investigators shall immediately report any changes to the clinical study that may have a material impact on the study conduct or increase the risk to subjects to the CRD, study site directors, and IRB.
14.3 Protocol amendments

(1) Under the following circumstances, the CRD shall conduct a review on whether the study should be continued at some or all of the study sites or on individual subjects according to the protocol, and shall amend the protocol where necessary.

(1) Upon learning of matters concerning the quality, efficacy, and safety of the investigational device or any other information that is material to the proper conduct of the study

(2) If change(s) to the protocol become necessary due to compelling medical circumstances

(3) When changing the main details of analysis described in the protocol (primary endpoints and analysis thereof)

(4) If the study site director issues an instruction to amend the protocol based on the advice of the IRB

(2) If the CRD decides that the protocol needs to be amended or changed, the investigators and CRD shall perform procedures based on the protocol preparation. The investigators and the CRD shall discuss and review the amendment(s) and agree on the amendment details (excluding amendments that pertain solely to clerical matter) and compliance therewith, and shall attest to this agreement by signing and dating the protocol or an alternative document.

15. Case Report Form (CRF)

15.1 CRF & pursuant forms used in this study

(1) CRF used in this study

1) ReoGo CRF

(2) Pursuant forms

1) ReoGo Data Clarification Form (DCF)

15.2 Points to note when preparing, changing or amending CRFs

The investigators shall promptly prepare a CRF for each subject after completion or discontinuation of the study in accordance with the 'CRF Manual', then sign and date the CRF and submit it to the CRD while also retaining a copy. If the subinvestigators prepared the CRF, the investigators shall check the details before submitting it to the CRD according to the aforementioned method, while also retaining a copy.

When entering data in the CRF based on source documents such as medical records and laboratory test printouts, the investigators or subinvestigators must ensure that the entered data does not contradict the source data. The investigators shall enter the reason(s) for any such discrepancies in the CRF or prepare a record of the discrepancy and enter it in the CRF.

The investigators or subinvestigators shall adhere to the 'CRF Manual' when changing or amending the CRF. When changing or amending the CRF, a double line shall be drawn through the previous entry and any changes or amendments shall be signed and dated by the person who
makes them. The investigators shall check any changes or amendments to the CRF performed by the subinvestigators and then attach their signature along with the date. The investigators shall also retain a copy of all CRF changes or amendments submitted to the CRD.

Study collaborators appointed by the study site director can only write in the CRF when transcribing original data.

Amendments and other items requiring confirmation that are approved by the CRD after collection of the CRFs will then be implemented using the 'Data Clarification Form' (DCF). Subinvestigators and study collaborators appointed by the investigators in the 'Job Assignment List' can fill out the DCF, provided that they also affix their signature. The investigator then signs and dates the completed DCF after checking the entered details and submits it to the CRD while retaining a copy.

15.3 CRF entries treated as original data

The following data appearing in the CRF will be regarded as original data.

1) AE severity, outcome, and determination of causal relationship with the investigational device intervention
2) Reasons for discontinuation and subsequent progress
3) Investigator and subinvestigator comments

16. Source Document Verification

The study site directors and investigators shall provide direct access to source documents and all other records relating to the study during monitoring, auditing, and surveys by the study site IRB.

17. Quality Control & Quality Assurance

Control of data quality will be done by managing all data according to the Standard Operating Procedure (SOP). Assurance of study quality will be achieved through system integration and data quality control and by monitoring these tasks to ensure they are performed properly.

The clinical research associate (CRA) will confirm that the study is being conducted in compliance with medical device GCP and the protocol, and verify that the CRF entries are consistent with the source documents. CRF entries that do not match the source documents, are inconsistent, or are illogical will be checked by the CRA and investigators to determine their validity, and the CRA may instruct the investigators to amend the CRF where necessary.

The data management supervisor (DMS) will then check the integrity of CRF entries pursuant to the SOP, and confirm that the database is accurate based on these entries.

The auditor will conduct an audit in accordance with the 'Medical Device GCP Auditing Regulations' and confirm/assess whether the clinical study system is properly constructed and that data quality control is being performed in an appropriate manner.
18. Ethics

18.1 Institutional Review Board (IRB)

(1) IRB review

Prior to commencement of the study, the IRB will conduct a review on the scientific and medical validity of the protocol, sample CRF, CEF, sample consent form, IB, documents explaining the subject's costs or compensation for injury to health, and the propriety of conducting the study.

(2) Review of study continuation

The IRB will review the propriety of continuing the study at each study site at least once a year or in the following circumstances.

1) When the CRD notifies the study site director of a serious, unforeseeable failure
2) When the investigators notify the study site director of an SAE
3) When the investigators inform the study site director of an amendment to the CEF
4) When the CRD informs the study site director of an amendment to the protocol, sample CRF, IB, or documents explaining the subject's costs or compensation for injury to health
5) When the investigators inform the study site director of a change to the investigators and/or subinvestigators
6) When materials deemed necessary by the IRB are amended

18.2 Ethical conduct of the study

This study shall be conducted in compliance with ethical principles based on the Helsinki Declaration, the study protocol, Articles 14-3, 14-4-4, 14-6-4, 80-2-1, 80-2-4, 80-2-5, and 82 of the Pharmaceutical Affairs Act, and the 'Ministerial Ordinance on Standards for the Conduct of Clinical Trials of Medical Devices (Medical Device GCP)' (MHLW Ministerial Ordinance No. 36, 2005).

18.3 Protection of subjects' human rights

The investigators or subinvestigators will carefully examine the propriety of seeking the participation of subjects after considering their health condition, symptoms, age, sex, capacity to consent, dependence on the investigators, and participation in other clinical studies from the perspective of protecting human rights and in accordance with the inclusion and exclusion criteria.

Identification of subjects at enrollment and in the CRF will be done using subject identification codes, while direct access to source data relating to the conduct of the study and subject consent forms, etc., as well as publication of clinical study results will be done in a manner that protects the privacy of subjects. Furthermore, the investigators, subinvestigators, study site personnel, and CRD are prohibited from divulging any information about the study to third parties.
19. Archiving of Records, etc.

(1) Study sites

The study site director will retain documents required to be archived at the study site for a period of 3 years from the date of study discontinuation or termination. However, the archive period and method will be determined by discussion with the CRD if the CRD deems it necessary to archive the records for a longer period. An archive manager will be appointed to perform the archiving of records.

(2) Institutional Review Board (IRB)

The founder of the IRB shall archive the SOP, list of IRB members (including the qualifications of each member), list of IRB member occupations and affiliations, submitted documents, summaries of meeting minutes and letters, etc., for a period of 3 years from the date of study discontinuation or termination. However, the archive period and method will be determined by discussion with the CRD if the CRD deems it necessary to archive the records for a longer period.

(3) CRD

The CRD will retain documents required to be archived for a period of 3 years from the date of study discontinuation or termination.

If documents being archived by the study director or founder of the IRB are no longer required to be archived, the CRD shall notify the study site director or the founder of the IRB via the study site director to that effect.

20. Remuneration & Insurance

20.1 Remuneration

When paying transport costs or other remuneration to subjects in order to alleviate the burden of participating in the study, the CRD shall allocate the payment to the study site, which will then pay the subject in accordance with its regulations.

20.2 Health injury compensation & insurance

(1) If a subject's health is injured by participating in the study, the study site will provide appropriate treatment and take all necessary measures, while the CRD will bear the subject's medical costs required for treatment minus any health insurance payments.

(2) If a subject's health is injured by participating in the study and a dispute or a potential dispute with a third party occurs as a result, the study site will immediately notify the CRD and attempt to resolve the dispute in cooperation with the CRD.

(3) The CRD will assume legal liability for damages arising from a health injury attributed to the study unless the study site was responsible for causing the injury. If the responsible party cannot be identified, the study site and the CRD will engage in bona fide discussions in an attempt to resolve the matter.

(4) The CRD will assume non-legal liability for damages arising from injury to health caused by the study. However, CRD will not pay compensation if: the injury was caused by the
study site; the injury is attributed to occasional cause; or a causal relationship with the study is ruled out. Compensation may be withheld or reduced if the injury arises as a result of the subject's willful or negligent conduct. The CRD shall fulfill its non-legal liability for damages in accordance with its own compensation procedures.

(5) The non-legal liability for damages described in the preceding paragraph shall be executed pursuant to the 'Relief System for Sufferers from Adverse Drug Reactions' stipulated by the MHLW.

(6) The CRD shall use insurance and other necessary measures as a means of fulfilling both its legal and non-legal liability for damages.

21. Publication of Study Results
The investigators and subinvestigators will obtain the written consent of the CRD before publishing any of the study results at conferences or in academic journals, etc.

22. Study Structure
1. Study representative
   Responsible for research operations and coordination to facilitate research.
   Principal

2. CRD
   Performs research operations.

3. Steering committee
   Prepares the protocol, CRF and CEF drafts, etc., and performs research operations and management. Makes all decisions concerning research operation and management.
   (1) Principal
   (2) Professor
   (3) Professor
   (4) Occupational therapist

4. Monitoring
   Clinical Development Department

5. Statistical analysis

6. Data management

7. Investigational device manager

8. Investigational device maintenance supervisor

10. Study site
   (1) Investigator
       Center director
   (2) Investigator
       Rehabilitation manager
   (3) Investigator
   (4) Investigator    Deputy director
   (5) Investigator    Deputy director
23. References
<table>
<thead>
<tr>
<th></th>
<th>Robotic therapy (n=30)</th>
<th>Self-guided therapy (n=26)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex (%)</strong></td>
<td>Male</td>
<td>21 (70.0)</td>
<td>18 (69.2)</td>
</tr>
<tr>
<td><strong>Age, years</strong></td>
<td></td>
<td>65.2 (10.9)</td>
<td>64.6 (11.5)</td>
</tr>
<tr>
<td><strong>Affected side (%)</strong></td>
<td>Non-dominant</td>
<td>20 (66.7)</td>
<td>12 (46.2)</td>
</tr>
<tr>
<td>Interval between stroke and randomization, days</td>
<td></td>
<td>47.8 (7.0)</td>
<td>46.9 (8.1)</td>
</tr>
<tr>
<td><strong>Type of stroke (%)</strong></td>
<td>Cardiogenic</td>
<td>2 (6.7)</td>
<td>4 (15.4)</td>
</tr>
<tr>
<td></td>
<td>Atherothrombotic</td>
<td>5 (16.7)</td>
<td>7 (26.9)</td>
</tr>
<tr>
<td></td>
<td>Lacunar</td>
<td>6 (20.0)</td>
<td>4 (15.4)</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>17 (56.7)</td>
<td>11 (42.3)</td>
</tr>
<tr>
<td><strong>OCSP class (%)</strong></td>
<td>LACI</td>
<td>7 (23.3)</td>
<td>6 (23.1)</td>
</tr>
<tr>
<td></td>
<td>TACI</td>
<td>3 (10.0)</td>
<td>2 (7.7)</td>
</tr>
<tr>
<td></td>
<td>PACI</td>
<td>20 (66.7)</td>
<td>18 (69.2)</td>
</tr>
<tr>
<td></td>
<td>POCI</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td><strong>Brunnstrom stage (%)</strong></td>
<td>III</td>
<td>19 (63.3)</td>
<td>16 (61.5)</td>
</tr>
<tr>
<td></td>
<td>IV</td>
<td>11 (36.7)</td>
<td>10 (38.5)</td>
</tr>
<tr>
<td><strong>Fugl-Meyer assessment</strong></td>
<td></td>
<td>29.1 (16.3)</td>
<td>31.8 (15.4)</td>
</tr>
<tr>
<td><strong>Wolf Motor Function Test</strong></td>
<td></td>
<td>69.4 (38.5)</td>
<td>65.9 (32.0)</td>
</tr>
<tr>
<td><strong>Motor Activity Log</strong></td>
<td>Amount of use</td>
<td>0.7 (1.0)*</td>
<td>0.6 (1.2)</td>
</tr>
<tr>
<td></td>
<td>Quality of movement</td>
<td>0.7 (0.9)</td>
<td>0.5 (1.0)</td>
</tr>
</tbody>
</table>

Data represent mean (SD), unless otherwise indicated.  
* One case could not be evaluated; therefore, this analysis was conducted on n=29.  
Table II: Changes in Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Robotic therapy group (n=30)</th>
<th>Self-guided therapy group (n=26)</th>
<th>Difference</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
<td>Difference</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean(SD)</td>
<td>Mean(SD)</td>
<td>Mean(SD)</td>
<td>Mean(SD)</td>
</tr>
<tr>
<td></td>
<td>Fugl-Meyer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper extremity</td>
<td>29.1 (16.3)</td>
<td>38.6 (16.0)</td>
<td>9.5 (7.9)</td>
<td>31.8 (15.4)</td>
</tr>
<tr>
<td>Proximal upper extremity</td>
<td>18.7 (9.0)</td>
<td>23.5 (7.8)</td>
<td>4.8 (5.0)</td>
<td>22.0 (7.7)</td>
</tr>
<tr>
<td>Flexor synergy</td>
<td>6.7 (3.9)</td>
<td>8.8 (3.1)</td>
<td>2.1 (2.7)</td>
<td>8.7 (2.8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Wolf Motor Function Test</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Performance time</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper extremity</td>
<td>69.4 (38.5)</td>
<td>52.7 (36.9)</td>
<td>-16.7 (19.5)</td>
<td>65.9 (32.0)</td>
</tr>
<tr>
<td>Proximal upper extremity</td>
<td>48.4 (42.8)</td>
<td>29.3 (32.7)</td>
<td>-19.1 (33.3)</td>
<td>33.8 (38.2)</td>
</tr>
<tr>
<td>Functional ability score</td>
<td>29.2 (16.1)</td>
<td>36.5 (17.5)</td>
<td>7.4 (10.6)</td>
<td>27.1 (15.3)</td>
</tr>
<tr>
<td></td>
<td>Motor Activity Log</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amount of use</td>
<td>0.71 (0.96)</td>
<td>1.17 (1.15)</td>
<td>0.46 (1.02)</td>
<td>0.58 (1.16)</td>
</tr>
<tr>
<td>Quality of movement</td>
<td>0.65 (0.86)</td>
<td>1.20 (1.23)</td>
<td>0.54 (0.92)</td>
<td>0.53 (1.02)</td>
</tr>
<tr>
<td></td>
<td>Simple Test for Evaluating Hand Function</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-affected side</td>
<td>88.3 (10.3)*</td>
<td>91.7 (7.2)</td>
<td>3.4 (7.1)</td>
<td>90.0 (10.3)</td>
</tr>
<tr>
<td>Affected side</td>
<td>3.6 (12.9)</td>
<td>15.0 (22.9)</td>
<td>11.4 (17.4)</td>
<td>4.3 (9.5)</td>
</tr>
<tr>
<td></td>
<td>Range of Motion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper extremity</td>
<td>954.3 (123.0)</td>
<td>932.0 (140.2)</td>
<td>-22.3 (111.5)</td>
<td>990.6 (121.9)</td>
</tr>
<tr>
<td>Proximal upper extremity</td>
<td>35.7 (35.5)</td>
<td>33.1 (26.3)</td>
<td>-2.6 (41.9)</td>
<td>27.5 (28.4)</td>
</tr>
<tr>
<td>Visual Analogue Scale</td>
<td>55.73 (17.41)</td>
<td>62.23 (17.08)</td>
<td>6.50 (10.97)</td>
<td>54.54 (18.46)</td>
</tr>
<tr>
<td>Motricity Index</td>
<td>3.63 (2.25)</td>
<td>3.53 (2.53)</td>
<td>-0.10 (2.26)</td>
<td>3.71 (1.67)</td>
</tr>
<tr>
<td></td>
<td>Functional Independence Measure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical items</td>
<td>61.1 (14.8)</td>
<td>73.6 (13.3)</td>
<td>12.6 (7.7)</td>
<td>62.2 (15.9)</td>
</tr>
<tr>
<td>Cognitive items</td>
<td>29.2 (5.0)</td>
<td>31.1 (4.0)</td>
<td>1.9 (2.4)</td>
<td>27.8 (6.9)</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>90.3 (18.4)</td>
<td>104.7 (15.8)</td>
<td>14.4 (8.2)</td>
</tr>
<tr>
<td></td>
<td>Brunstrom Stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>1 (3.3)</td>
<td>1 (3.3)</td>
<td>...</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>III</td>
<td>15 (30.0)</td>
<td>13 (43.3)</td>
<td>...</td>
<td>16 (61.5)</td>
</tr>
<tr>
<td>IV</td>
<td>13 (43.3)</td>
<td>9 (30.0)</td>
<td>...</td>
<td>10 (38.5)</td>
</tr>
<tr>
<td>V</td>
<td>1 (3.3)</td>
<td>7 (23.3)</td>
<td>...</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

*Wilcoxon rank-sum test,  n=29*
Table III: Changes in WMFT score (baseline vs. post-intervention)

<table>
<thead>
<tr>
<th>Change in WMFT total$^a$</th>
<th>Robotic therapy group (n=30)</th>
<th>Self-guided therapy group (n=26)</th>
<th>$P^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased</td>
<td>15 (3.3%)</td>
<td>15 (3.8%)</td>
<td>0.93</td>
</tr>
<tr>
<td>Unchanged</td>
<td>355 (78.9%)</td>
<td>305 (78.2%)</td>
<td></td>
</tr>
<tr>
<td>Increased</td>
<td>80 (17.8%)</td>
<td>70 (18.0%)</td>
<td></td>
</tr>
<tr>
<td>$P^b$</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Change in WMFT proximal$^a$</th>
<th>Robotic therapy group (n=30)</th>
<th>Self-guided therapy group (n=26)</th>
<th>$P^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased</td>
<td>10 (4.8%)</td>
<td>10 (5.5%)</td>
<td>0.05</td>
</tr>
<tr>
<td>Unchanged</td>
<td>156 (74.3%)</td>
<td>149 (81.9%)</td>
<td></td>
</tr>
<tr>
<td>Increased</td>
<td>44 (20.9%)</td>
<td>23 (12.6%)</td>
<td></td>
</tr>
<tr>
<td>$P^b$</td>
<td>&lt;0.001</td>
<td>0.02</td>
<td></td>
</tr>
</tbody>
</table>

WMFT, Wolf Motor Function Test

$^a$Scores were categorized as $\geq120$ s (0) or $<120$ s (1), and change in score was categorized as increased (0 to 1), decreased (1 to 0), or unchanged (0 to 0 or 1 to 1). Numbers indicate the number of task items (%).

$^b$McNemar test

$^c$Two-sample Wilcoxon test
Table IV: Adverse events and serious adverse events

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>Robotic therapy group (n=30)</th>
<th>Self-guided therapy group (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious adverse events, n (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Adverse events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Related to study therapy, n (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Unrelated to study therapy, n (%)</td>
<td>18 (60.0)</td>
<td>17 (56.7)</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>2</td>
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<tr>
<td>Psychiatric disorders</td>
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<td>1</td>
</tr>
<tr>
<td>Nervous system disorders</td>
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<tr>
<td>Vascular disorders</td>
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<tr>
<td>Respiratory, thoracic, and mediastinal disorders</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>6</td>
<td>6</td>
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<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>3</td>
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<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>6</td>
<td>8</td>
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<tr>
<td>Renal and urinary disorders</td>
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<td>0</td>
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<tr>
<td>General disorders and administration site conditions</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Increase of serum amylase</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Injury, poisoning, and procedural complications</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

The principal investigator at each site determined whether an adverse event or serious adverse event was related to the intervention. Adverse events are listed according to the organ-classification system used in the Medical Dictionary for Regulatory Activities.