Virtual Reality Glove for Hand and Arm Rehabilitation After Stroke

Study Protocol and Statistical Analysis Plan

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PROTOCOL TITLE

vREHAB

Virtual Reality Glove for Hand and Arm RehaBilitation

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vREHAB

AGREEMENT ON THE PROTOCOL

By signing below, I confirm that:

1) I have read this protocol and it contains all necessary details for conducting this study

AND

2) I agree to conduct the trial in compliance with this protocol and to adhere to all regulations that govern the conduct of the study.

_____ _____

Principal Investigator's Signature **Date**

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Principal Investigator's Name

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Site Name:

The *Virtual Reality Glove for Hand and Arm RehaBilitation* (vREHAB) trial is a randomized, controlled, phase 2 trial aiming to evaluate the safety, usability, and efficacy of a virtual reality biofeedback system (Neofect RAPAEL Smart Glove) to promote recovery of distal arm and hand function after stroke, as compared to standard of care therapy. The purpose of the study is to demonstrate (a) the feasibility of increasing the dose of rehabilitation in acute stroke patients with the Smart Glove, (b) the effect of Smart Glove use on functional recovery, and (c) the effect of Smart Glove use on quality of life.

Background

Every year, over 700,000 patients in the US suffer from stroke. Upper extremity impairment is very common after stroke, with 15-30% of stroke survivors experiencing long-term arm weakness (1). Distal upper extremity strength is required to complete a number of activities of daily living (ADLs), including feeding, grooming, dressing, writing, and typing. As such, impairment of arm function limits patients' ability to become independent in ADLs, resulting in significant costs, burden on caregivers, and a negative impact on patients' quality of life (QOL) after stroke (2). However, even after intensive rehabilitation of the upper extremity, only 5-20% of patients achieve complete functional recovery (3).

Despite the major public health, as well as personal, costs resulting from impaired arm function after stroke, treatment options are limited. The best evidence exists for constraint induced movement therapy (CIMT) and robotic therapy (4). Constraint induced movement therapy involves immobilization of the non-paretic arm for 90% of waking hours and high-repetition task-oriented training for at least six hours per day. This therapy is not widely used due to its many limitations including the need for high intensity supervision by a therapist and patients' frustration with the therapy. Robot assisted arm training involves either passive movement of the affected arm or active movement with partial assistance. A meta-analysis has shown that robotic use leads to improvements in strength and ability to perform ADLs (4). Robots are, however, not widely used because they are expensive, large, not widely available, and need specific expertise to operate.

With the increasing affordability and accessibility of virtual reality (VR) systems, VR has emerged as a new platform for stroke rehabilitation. VR therapy involves using computer-based programs to simulate daily tasks and events. VR has shown promise in both allowing patients to practice activities that directly translate to their ADLs, as well as motivating them by providing a novel and interesting virtual environment. A recent Cochrane Review of VR-based rehabilitation interventions concluded that it may be beneficial in improving upper limb function and ADL function, though it is unknown if these gains are sustained in the long term (5).

The aim of this research is to test a novel VR-based rehabilitation method, Smart Glove therapy, for recovery of arm function. Smart Glove therapy adopts the features that make constraint induced movement therapy and robotic therapy effective but does not have the same limitations. Specifically, the Neofect Smart Glove, like constraint induced movement and robotic therapy, promotes high frequency, intensive, repetitive movement therapy, features that have been shown to promote neuroplasticity and functional recovery (7). Unlike CIMT and robotic therapy, the Smart Glove is portable and therefore well-suited for home-use. It has an intuitive user interphase and therefore does not need supervision by an occupational therapist, uses games that can be played at different levels of complexity to keep patients engaged and motivated as their arm function improves, and is low-cost.

The Neofect Smart Glove is a commercially available, non-invasive biofeedback based system for distal upper extremity rehabilitation. The Smart Glove is very lightweight and allows for easy movement of all distal upper extremity joints. It consists of a glove-shaped sensor device and a software application which can be used with either a large screen or a portable tablet. It is made of an elastomer material that is simple to maintain and clean. The Bending Sensor, which consists of 3 acceleration channels, 3 angular rate channels, and 3 magnetic field channels, can detect wrist movement and position along 9 axes, and the amount of individual finger movements can also be precisely sensed by the glove (**Figure 1-3**).

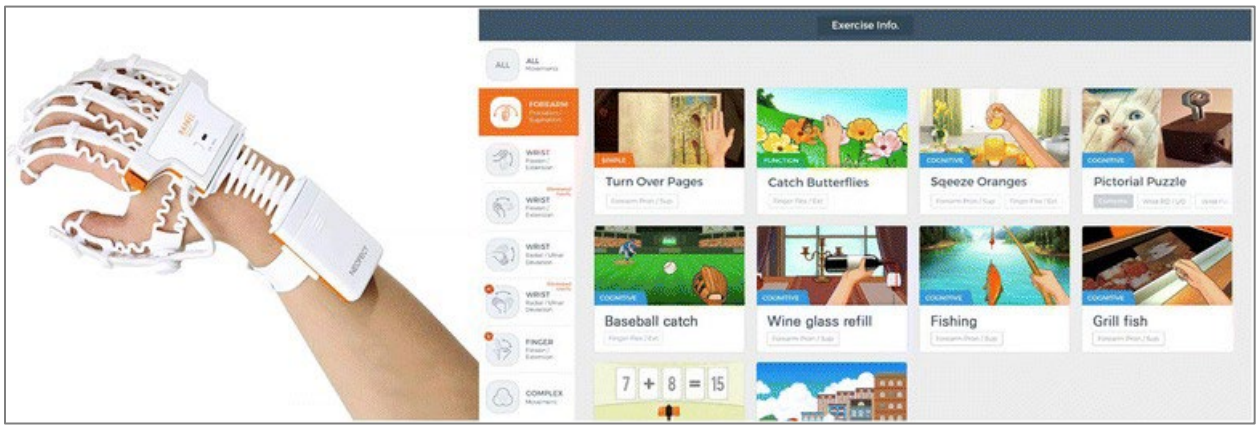

Figure 1: *The RAPAEL Smart Glove™ system and the task-specific games of this system*

The system includes multiple ADL-based training games, and the system tracks the motion and posture of the wearer's distal limb as they participate. Games can be selected to focus on certain movements (such as forearm pronation/supination, wrist flexion/extension, finger flexion/extension, etc.) based on the needs of the wearer. The software includes a smart learning algorithm, in which the computer automatically adjusts to the optimal level of difficulty to balance challenge and motivation. After initial set-up, the device requires no therapist supervision to use.

Figure 2: *The Smart Glove*

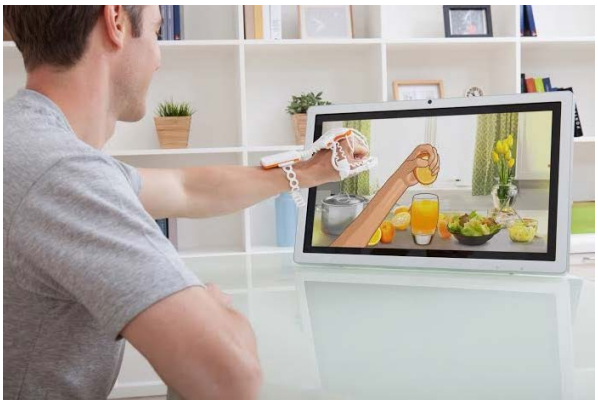

Figure 3: *Using the Smart Glove in the VR environment*

Preliminary data: A meta-analysis of 72 VR-based stroke rehabilitation studies has shown that VR may be beneficial in improving upper limb function and activities of daily living when used in

combination with usual care.(4) This analysis showed a trend towards better outcomes with a higher dose of VR therapy and with customized rehabilitation systems as opposed to systems primarily designed for gaming. The study did not report specifically on the effect of VR therapy on wrist and hand function.

A recent single-blinded, randomized controlled trial of 46 stroke survivors compared the Smart Glove combined with standard occupational therapy (OT) to dose-matched conventional upper extremity OT. Patients assigned to the Smart Glove used the Smart Glove in a rehabilitation facility under supervision of a therapist. The primary outcome was change in the Fugl-Meyer (FM) assessment, with secondary outcomes including fine motor tasks and quality of life (QOL). The study found an improvement of 5.3 points on the Upper Extremity Fugl-Meyer score in the active treatment group versus 1.3 points improvement in the control group ($p<0.001$) as well as greater improvements in fine motor tasks, assessed with the Jebsen Taylor Hand Function test, and QOL in the Smart Glove group.(6)

We recently concluded a 20-patient feasibility study at Stanford with the Smart Glove in subacute and chronic stroke patients who used the device at home without supervision. Patients were issued the device for an eight-week period and asked to use the device for 60 minutes per day for five days per week in their home environment. We demonstrated that it is feasible for patients to use the Smart Glove without direct supervision and learned that 60 minutes of Smart Glove therapy per day was too long for most patients. Based on these results, we feel comfortable that the current proposal, which specifies unsupervised home-use for 30 minutes per day, is achievable. The fact that the feasibility study was completed ahead of schedule and that all patients returned for their follow-up visits indicates that our study design does not place undue burden on the subjects or research coordinators. Importantly, we showed improvements in hand function (decrease in Jebsen Taylor Hand test times) and arm mobility (improvement in Fugl-Meyer score) after 8 weeks of use in our feasibility study (**figure 4**). These results are encouraging as these were chronic stroke patients who had plateaued in terms of their recovery prior to the Smart Glove intervention.

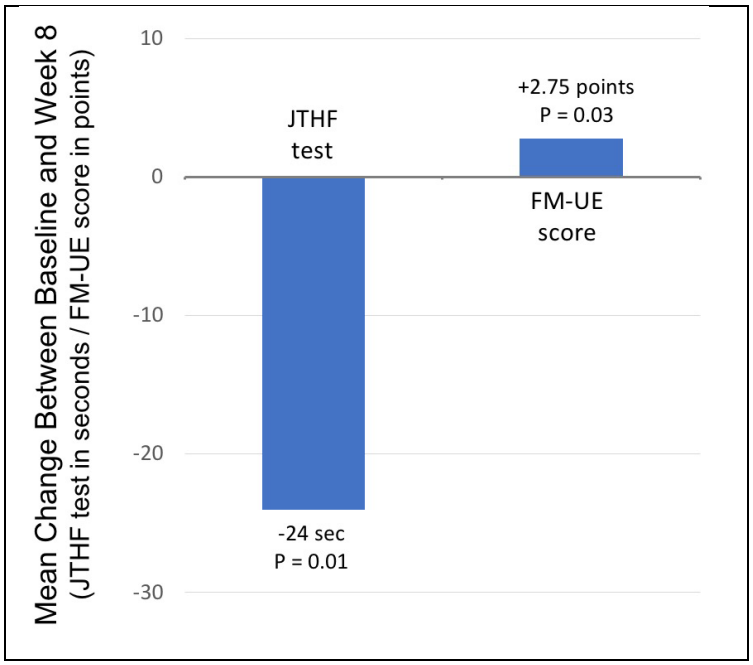

Figure 4. An 8-week therapy program with the Neofect Smart Glove in chronic stroke patients showed improvement in hand function on the Jebsen Taylor Hand Function (JTHF) test and in arm mobility on the Fugl Meyer Upper Extremity (FM-UE) score.

While these preliminary studies show promising results, important questions remain unanswered. These include: Can patients use self-guided Smart Glove therapy in their home or rehabilitation environment in addition to their routine rehabilitation therapy in the sub-acute

stroke period? Is the addition of Smart Glove therapy to routine rehabilitation therapy beneficial for recovery of arm and hand function? We will address these questions in the vREHAB study.

Primary Hypothesis
Our hypothesis is that self-directed use of the Smart Glove is feasible for subacute as well as chronic stroke patients, results in an increased dose of upper extremity rehabilitation, and leads to improved functional outcome and quality of life for stroke survivors.

Specific Aims

Aim 1: Demonstrate the feasibility of increasing the dose of rehabilitation in acute stroke patients with the Smart Glove. We hypothesize that patients randomized to the Smart Glove will have more upper extremity therapy than patients randomized to standard of care therapy.

Aim 2: Demonstrate the effect of Smart Glove use on functional recovery. We hypothesize that patients randomized to Smart Glove will have a greater improvement in arm/hand function as assessed on the Jebsen Taylor Hand Function (primary efficacy outcome) and Fugl-Meyer tests at the end of the intervention period, and that this improvement is sustained 12 weeks after completion of the intervention.

Aim 3: Demonstrate the effect of Smart Glove use on quality of life. We hypothesize that, compared to controls, patients randomized to Smart Glove will have a greater improvement in self-rated stroke related disability and quality of life (assessed with the Stroke Impact Scale) at the end of the intervention period, and that this improvement is sustained 12 weeks after completion of the intervention.

Relevance
Regaining upper extremity function is very important for stroke survivors to increase their independence and ability to perform ADLs. The large majority of outpatient stroke rehabilitation currently takes place in a therapy clinic; however, access is often limited by resource allocation, financial hardship, and transportation difficulties. The Smart Glove is unique in its portability, ease of use, and low cost. It could easily be provided to stroke patients with limited financial resources and, because of its portability, can be shipped to patients in more geographically remote areas who have limited access to regular therapy services. Thus, if successful, this research could lead to a novel rehabilitation method that provides value-based care to a large proportion of stroke patients with impaired arm function.

Study Sites
Stanford University will be the Coordinating Center for this study. Patients will be recruited from the Inpatient Stroke Unit, the Outpatient Stroke Clinic, or Stanford-affiliated Acute Rehabilitation Units. Stanford's CTRU and the Neurology Outpatient Clinic will be used for study visits and assessments. Other non-Stanford affiliated sites will be invited to participate and will require separate IRB approval per their institution. A total of 80 patients will be included.

Patient Population
Patients will be eligible for the study if they (1) have a history of an ischemic or hemorrhagic stroke and (2) have impaired arm/hand function secondary to the stroke (see below for specific inclusion and exclusion criteria). We will recruit 40 patients over a 4-year period at Stanford's acute care hospitals, acute rehabilitation units, and outpatient facilities. The doctor and/or research coordinator may introduce the study to potential candidates in-person in the aforementioned sites, and the research coordinator may contact potential candidates by phone after the doctor's referral. Enrolled patients will be randomized (1:1 ratio) to standard

rehabilitation therapy versus standard rehabilitation therapy plus Smart Glove use. All patients will be allowed to participate in any scheduled outpatient rehabilitation during the study. Patients who are randomized to the Smart Glove treatment arm will take the Smart Glove with them if they transition between facilities; for example, if they transition from the acute hospital to an acute rehabilitation facility or to home.

Inclusion Criteria:
(1) a diagnosis of ischemic or hemorrhagic stroke
(2) unilateral hand/arm weakness from stroke with indication for upper limb rehabilitation therapy.
(3) ability to successfully play 2 out 4 pre-selected test games with the Smart Glove. The test specific games and criteria for passing are as follows:
- Pour the wine (Pronation/Supination): **make 5 pours in first 1 minute**
- Snow Ball Fight (Wrist Flexion/Extension w/ gravity eliminated): **take down 3 objects in first 1 minute**
- Scrub the Floor (Wrist Radial/Ulnar deviation w/ gravity eliminated): **scrub the floor 5 times in first 1 minute**
- Float the Fish (Finger Flexion/Extension): **make 50 meters with 3 or less bumps in first 3 minutes**

Exclusion Criteria:
(1) Age <18 years
(2) history of visually provoked seizures.
(3) psychological disorder that could impede participation.
(4) pre-existing neurologic disorder which causes significant deficits in arm/hand function (e.g. Parkinson's disease, peripheral neuropathy, etc.).
(5) severe receptive aphasia which results in inability to participate with the Smart Glove.
(6) cognitive impairment which results in inability to participate with the Smart Glove.
(7) severe pain impeding upper extremity rehabilitation and use of the Smart Glove.
(8) limited life-expectancy which makes it unlikely that patient will be able to complete the 24-week follow-up visit
(9) any medical or other condition that, in the opinion of the investigator, makes the patient unsuitable for participation in this study.

Randomization: Once the participant has given informed consent and enrolled in the study, they will be randomized in a 1:1 ratio to Smart Glove therapy plus usual care versus usual care alone. A dynamic stratification system will ensure well-balanced subgroups. The randomization algorithm will employ biased-coin minimization and the variance method with stratification weights (8). The strategy is to balance treatment assignment along the marginal distribution of each stratification factor. The stratification factors used, will be: 1) age, 2) time from symptom onset to enrollment, 3) finger extension muscle testing score at enrollment, and 4) study site.

Study Procedures: The study consists of a 12-week intervention period and a 12-week follow-up period. During the 12-week intervention period all patients will receive their usual rehabilitation therapy, with their therapists documenting rehabilitation dose in a journal provided at the start of the study. In addition, subjects randomized to the Smart Glove therapy arm will be provided with a Smart Glove system, which includes the glove and tablet. The subjects will be trained on how to don and doff the glove, pair the glove and tablet, and start the smart algorithm to progress through games appropriate to the subject's current functional status. Subjects will be instructed to use the system for at least one session per day for 5 days per week during the 12-week intervention period. During this period, the device's learning schedule

algorithm will automatically adjust the daily therapy sessions to the optimal level of difficulty to balance challenge and motivation. Each session typically takes 20-30 minutes depending on the patient's speed. Study coordinators will be readily available for any technical troubleshooting needs. Participants will all receive phone calls by coordinators during weeks 1-5, and 7-11, to ensure compliance and troubleshoot as needed, and will present for in-person visits on weeks 6, 12, and 24 for blinded assessments by study coordinators. Smart Glove usage data from participants in the intervention arm will be monitored and dose of rehabilitation as recorded on the PT/OT rehabilitation log will be reviewed and documented on CRFs during in-person visits.

At the completion of the intervention period, subjects will return the Smart Glove and subjects in both arms of the study will only receive usual care during the 12-week follow-up period. They will continue to record any rehabilitation they receive during this time period. Participants will continue to receive phone calls by coordinators during weeks 13-24 to ensure compliance with rehabilitation logging. Subjects will have a final assessment at week 24 (12 weeks after completing the intervention) to assess for persistence of effect. After the final assessment, at study completion, all individuals who were randomized to the standard therapy arm will be offered use of the Smart Glove, at no cost to the patient, for a period of 6 weeks.

An overview of the study assessments is described below and summarized in table 1.

Day 0, baseline visit:

- Research coordinator will review the research consent form in detail with the participant and answer any questions about the study. After informed consent, the participant will be enrolled in the study, and baseline demographics will be collected.
- Smart Glove training for patient and caregiver
- Issuance of Smart Glove and tablet with preloaded software
- Modified Rankin Scale and NIHSS scoring
- Baseline testing of the affected extremity:
    - Jebsen-Taylor hand function test (JTHFT)
    - Upper Extremity Fugl-Meyer assessment (FM)
    - Manual muscle testing (MMT)
    - Shoulder Abduction/Finger Extension (SAFE) score of Predicting Recovery Potential (PREP) algorithm → 72h post-stroke (retrospective) and at enrollment

Day 7, 14, 21, 28 and 35:

- Phone call for patient compliance and troubleshooting

Day 42, follow-up visit #1 (mid-intervention):

- Discussion regarding patient compliance and troubleshooting
- Document amount of rehabilitation from PT/OT session log
- Testing of the affected extremity:
    - Fugl-Meyer assessment (FM)
    - Jebsen-Taylor hand function test (JTT)
- Download of patient use data from tablet (SmartGlove arm only)

Day 49, 56, 63, 70 and 77:

- Phone call for patient compliance and troubleshooting

Day 84 follow-up visit #2 after routine clinical follow-up appointment (end-intervention):

- Assess amount of rehabilitation from PT/OT session log
- Modified Rankin Scale

- Testing of the affected extremity and quality of life:
  - Jebsen-Taylor hand function test (JTHFT)
  - Fugl-Meyer assessment (FM)
  - Manual muscle testing (MMT)
- Stroke Impact Scale (SIS)
- Download of patient use data from tablet (SmartGlove arm only)
- User experience survey (SmartGlove arm only)

Day 91, 98, 105, 112, 119, 126, 133, 140, 147, 154, 161:

- Phone call for patient compliance and troubleshooting

Day 168 follow-up visit #3 (end-study):

- Assess amount of rehabilitation from PT/OT session log
- Modified Rankin Scale
- Testing of the affected extremity and quality of life:
  - Jebsen-Taylor hand function test (JTHFT)
  - Fugl-Meyer assessment (FM)
  - Manual muscle testing (MMT)
- Stroke Impact Scale (SIS)

Table 1. Schedule of Events

Time-point	Week 0	Weeks 1 – 5	Week 6	Weeks 7 – 11	Week 12	Weeks 13 – 23	Week 24
Informed Consent	X						
Demographics	X						
Medical History	X						
Compliance Phone-Calls		X		X		X	
SAFE score (at 72h and at enrollment)	X						
Modified Rankin Scale (mRS)	X				X		X
NIHSS assessment	X						
Jebsen Taylor Hand Test (JTHT)	X		X		X		X
Upper Extremity Fugl-Meyer (FM)	X		X		X		X
Manual Muscle Testing (MMT)	X				X		X
Stroke Impact Scale (SIS)					X		X
Assess amount of rehabilitation			X		X		X
User Survey (Smart Glove arm)					X		

Data analyses: All efficacy analyses are analyzed under the intention to treat principle. The primary efficacy outcome is the change in score on the Jebsen Taylor Hand Test between baseline and week 12. Secondary efficacy endpoints are changes in scores on the upper extremity Fugl-Meyer Scale, modified Rankin Score, total NIHSS score, Manual Muscle testing (of the biceps, triceps, wrist extensors, finger flexors, and finger abductors), Stroke Impact Scale, and total dose of rehabilitation received during the 12-week intervention period. Persistence of the treatment effect will be tested by comparing changes in scores on the Jebsen Taylor Hand Test and Fugl-Meyer upper extremity score at 24 weeks between treatment groups. Differences between treatment groups will be assessed using a generalized linear model (GLM) that accounts for repeated measures (assessments at baseline, 6 and 12 weeks for primary outcome, as well as 24 weeks for secondary outcome) and will be adjusted for imbalances in baseline variables. We will use a two-sided test with an alpha of 0.05 to declare significance. Based on prior studies we assume to see an 11.0-point improvement on the JTHF

test in patients who use the glove, a 3.0-point improvement in control subjects, and a standard deviation of the change score of 2.0.(1) Based on these assumptions we will have more than 90% power to show a significant effect of the use of the Smart Glove on our primary efficacy outcome.

Risks
Potential risks and inconveniences include that the participant will need to travel to Stanford for 3 follow-up visits over the course of the study. One may also experience technical difficulties in using the Smart Glove system. There is a low likelihood of one having a skin reaction to the material used to make the Smart Glove.

Benefits
While there is no definitive evidence that SmartGlove therapy will benefit patients, a potential benefit is that the participant may experience improvement in the function of their affected upper extremity as a result of study participation.

Withdrawal
Each subject and the investigator reserve the right at any time to terminate a subject's participation in the clinical investigation. Possible reasons for study withdrawal:

1) Subject voluntarily withdraws consent
2) Subject develops an adverse event that would not allow him or her to continue in the study
3) Subject has an adverse event which, in the opinion of the investigator, warrants withdrawal from the study. The sponsor or its designee must be notified within 2 business days
4) A decision is made by the subject and/or investigator that the subject should be withdrawn from the study

Alternative to Participation:
There are several alternatives to participation that each potential study candidate should discuss with their physician. The alternatives include not participating and seeking no other treatment, or not participating and seeking a standard-practice treatment which is outpatient occupational therapy. Candidates should understand that choosing to participate is not mutually exclusive with receiving outpatient occupational therapy.

Data Collection, Transfer, and Storage
Clinical assessments (UE-FM, MMT and JTHT) will be done by an investigator blinded to treatment assignment. All study data (including patient demographics, previous medical conditions, mRS, NIHSS, MMT, FM, JTHT, and SIS scores) will be entered directly on electronic case report forms (eCRFs) programmed in RedCap, a HIPAA compliant electronic clinical trial database. For patients randomized to the Smart Glove arm, time of use of the device and performance on the VR games will be collected automatically by the device and downloaded at the aforementioned time points during the intervention period. Screening logs will be kept of patients who are considered but not enrolled in this trial and the reason for exclusion will be recorded.

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