# Study Overview

STUDY TITLE: Dopaminergic enhancement of rehabilitation therapy early after stroke

INSTITUTIONAL REVIEW BOARD (IRB) #: 22-000104

DESCRIPTION: Telerehabilitation (TR) is defined as delivery of rehabilitation services via communication technologies. This study uses an established TR system and protocol to supplement usual care, and also asks whether adding a dopaminergic drug enhances TR effects. In addition, the predictive value will be examined for two biomarkers that characterize capacity for brain plasticity.

Patients with arm weakness due to a new stroke in the past 30 days will be randomized to receive [1] 6 weeks of TR + Sinemet 25/100 once/day, on top of usual care (UC), [2] 6 weeks of TR + placebo once/day, on top of UC, or [3] UC alone. TR consists of 70 minutes/day of activity targeting upper extremity (UE) function, delivered in the home and (when appropriate) initiated in the inpatient rehabilitation facility (IRF) setting. Two previously validated predictive biomarkers are hypothesized to prospectively identify treatment responders: first, extent of stroke-related injury to the corticospinal tract (CST), obtained via MRI scan; and second, a polygene score focused on dopamine neurotransmission.

The currently planned study uses very similar software and hardware as the TR system as in a prior national study that found that this TR system was safe, associated with significant gains in arm function[3] and in global function[14], and had efficacy comparable to that seen when the same dose of therapy was delivered in the clinic (i.e., delivered in the same manner as standard care). In that prior study, the FDA determined (Q140628) that the investigation was a non-significant risk device study.

## STUDY AIMS:

Aim 1. TR+UC is superior to UC alone: A 6-week program of TR targeting arm movement added to UC will result in better arm function as compared to UC alone. The primary endpoint is the change in Action Research Arm Test (ARAT) from baseline to 1 month after end of therapy.

Aim 2. TR+Sinemet is superior to TR+placebo: Among patients randomized to TR, gains in arm function will be greater in those who take Sinemet (25/100) each day prior to TR, as compared to patients who take placebo each day prior to TR.

Aim 3. Less CST injury and higher dopamine polygene score predict better recovery of arm function: Across all subjects, change in arm function will be highest in those with lower % CST injury and in those with higher dopamine polygene scores. These relationships will remain significant when examining only patients randomized to TR. The drug X gene score interaction term will be significant such that the slope of arm gains in relation to the polygene score will be smaller (less steep) in those receiving Sinemet.

# Contact Information

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# Background

**Patients need higher doses of high-quality rehabilitation therapy**: Stroke remains a leading cause of human disability. Motor deficits are a substantial contributor to this, particularly in the arm: few patients fully recover from arm weakness after a stroke, with the remainder demonstrating persistent arm impairments that are directly linked to larger activity limitations and participation restrictions, lower quality of life, and decreased well-being[15-17]. Increasing evidence suggests that intensive activity-dependent therapy can improve outcomes after stroke[18-22]. However, most patients do not receive intensive therapy for reasons that include difficulty traveling to a provider (particularly in the COVID-19 era), shortage of regional rehabilitation care, and poor compliance with assignments.

The amount of rehabilitation therapy received as part of UC is generally small and inconsistent. During the acute stroke admission, the dose of occupational therapy (OT) and physical therapy (PT) provided to a patient varies widely across hospitals[23]. After discharge from the acute admission, the type, location, and dose of rehabilitation therapy are also highly variable[24-29].

This is also true in the outpatient setting, where provision of OT and PT after a stroke remains sparse and inconsistent. A study of 23,413 U.S. patients found that during the first 30 days after discharge from the acute stroke admission, 59% did not see an OT or PT at all[30]. A later study of 6,743 adult stroke survivors in the U.S. found that 67% of patients did not receive any outpatient rehabilitation therapy[31]. Medicare generally pays for very few outpatient OT and PT sessions[32]. Outpatient therapy is provided in an inconsistent way[31, 33], despite the fact that outpatient therapy after stroke has the potential to improve functional status, survival, and quality of life; and to reduce the risk for several psychological disorders[15, 31, 34-36]. Furthermore, even when patients can access stroke rehabilitation, the amount of therapy provided in standard of care is limited[4, 37-40], averaging just 32 arm movements/session[4], vastly lower than the 600-924 movements/session deemed necessary in animal studies[41-43].

The quality of rehabilitation therapy is also important and can increase the extent to which clinical neuroplasticity is harnessed[44]. Effects are increased when therapy is challenging, motivating, and engaging[1, 45-48].

**The promise of a telehealth approach for increasing rehabilitation therapy**: Telehealth approaches have the potential to improve the quantity and quality of rehabilitation therapy after stroke. A telehealth approach can increase access to rehabilitation therapy[31]. A telehealth approach also increases the quality of rehab therapy by boosting motivation and thus improving patient compliance.

TR is the delivery of rehabilitation services via communication technologies[49]. TR therapy is delivered by a licensed therapist via a computer and over the internet and can occur either synchronously (i.e., live interactions between therapist and patient) or asynchronously (i.e., the patient works alone and the therapist reviews performance later). TR follows the same

principles of traditional, person-to-person, individualized rehabilitation care. Such telehealth therapy provides a powerful supplemental option to brick-and-mortar delivery of rehabilitation services[50-53], reducing the need for impaired patients to travel and increasing access to care by clinicians familiar with stroke rehabilitation, an option useful in regions with a shortage of providers. These potential advantages are particularly important in the COVID era. As such, even if benefits of TR over usual care (UC) are modest, TR could be of value to many patients as an alternative means to access rehabilitation therapy.

Because TR incorporates a computer, therapy can be provided via games, which promote patient participation in health care[5-9]. Games motivate patients to engage in enjoyable play behavior that involves therapeutically relevant movements[10, 11], important because patient compliance is often low when stroke rehabilitation is delivered through traditional methods[54-56]. TR can also reduce the burden on caregivers and increase compliance; costs might also be lower[57] but this issue will not be examined in the currently proposed clinical trial.

**Mounting evidence that TR helps with motor deficits after stroke**: Increasing data support the utility of motor TR. A recent meta-analysis reported that all 18 studies of post-stroke motor TR improved motor disabilities[53]. Another noted that effects of TR did not differ from those seen with in-person rehabilitation or UC, although findings from this review must be viewed cautiously given that the authors defined TR quite broadly (e.g., including interventions that relied on phone calls, a DVD, email, or an online chat room)[58]. Other reviews indicate that higher TR usage results in greater benefit[59], although to date many studies have been small and uncontrolled[53, 59-62]. In one recent review of neurotechnological interventions for upper-limb motor rehabilitation, Coscia et al[63] stated

*"We also promote the necessary conceptual change from 'one-suits-all' treatments within inpatient clinical rehabilitation set-ups towards personalized home-based treatment strategies by adopting novel technologies…."*

In this regard, it is important to note that the current proposal employs a telehealth intervention that fosters a personalized treatment plan, is structured and therapist-supervised, maintains an ongoing relationship between therapist and patient[1], is designed for use in the home[64], and directly emulates the successful approach used in our prior national TR trial[3].

**The active ingredients in the current telehealth approach:** It is important to characterize the therapy that is delivered using telehealth methods. The active TR ingredients underlying the substantial behavioral gains seen in our national trial[3] can be summarized using the Rehabilitation Treatment Specification System (RTSS)[65, 66].

The main treatment targets promoted by the therapist and by TR system usage include five skills and habits: [1] improved UE motor function; [2] increased activity throughout the day (i.e., when not using the TR system); [3] increased capacity for sustained attention; [4] maintenance of a structured daily rehabilitation practice; and [5] healthier lifestyle choices. Treatment

targets also include three representations [1] improved mood, confidence, and quality of life; [2] increased knowledge about stroke; and [3] increased fun.

The main direct target[65] is improved UE motor function, which arises from CNS motor system plasticity and to a lesser extent from improved UE muscle strength; improved UE motor function is thus the main skill improved by TR and is captured by serial ARAT scoring.

The main volitional target[65] (i.e., the main accessible/verifiable measure of patient behavior that occurs without direct therapist supervision) is maintenance of a structured daily rehab practice, measured through daily usage statistics automatically calculated by the TR system and provided to patient and therapist.

The dosing parameter is a daily 70-min therapy session, created by the patient's treatment therapist, which includes 65 min of activity-based arm motor therapy (functional games and exercises) plus 5 minutes of stroke education, all of which involve targeted arm movement. The target TR dose for treatment therapists to assign is >800 arm movements/day, considerably higher than the 32 repetitions/session in routine clinical care[4].

Patient performance of many repetitions of activity-dependent therapy targeting the paretic arm is at the core of this TR program. The games in the TR system stress many different behaviors as part of motor training (e.g., memory load, sustaining a movement, movement precision, accurate timing of movement, and visuomotor tracking of a target).

The biological model underlying treatment efficacy, therefore, is that UE motor repetitions performed during TR activate numerous brain circuits including memory, attention, somatosensory, visuomotor, and cognitive circuits to drive motor cortex, with convergence of output on the CST. For example, in the "Clay Shooting" game, the patient uses the UE to track a flying clay pigeon, activating the dorsal and lateral reaching systems[67]. In the "Target" game, the patient squeezes a force transducer to keep the cursor within increasingly narrow brackets, activating sensorimotor and reward circuits[68]. In the "Slots" game, the patient must time button pushes to line up the same image on three successive reels; activating error-detection networks[69].

The motor-related circuits activated by TR use have in common reliance on CST as the effector pathway, and so the model also suggests that a measure of CST injury will be a useful biomarker of treatment-related gains. While there are multiple CSTs arising from primary and secondary motor cortices, the focus here will be on CST arising from primary motor cortex; secondarily, we will also examine injury to CSTs arising from secondary motor, as we have done previously[70].

**The rationale for using this 6-week (42-hour) program of therapist-supervised, home-based TR**: This dose and this approach proved to be an effective therapy in the national trial[3], and so treatment dose and content will not be modified in the currently proposed study. The prior national trial found that 6 weeks of TR was safe and associated with substantial gains in

UE-FM, Box & Blocks, and mRS scores, among all patients. This was also true among those patients who were enrolled >90 days post-stroke, a timepoint where spontaneous motor recovery after stroke has generally reached a plateau and thus any gains are very likely attributable to the intervention itself[3, 14]. Given this evidence that the intervention is effective at improving arm function, current goals do not aim to change the intervention but instead to compare it to a control, UC alone, and to evaluate its efficacy when a dopaminergic drug is introduced prior to each day's TR session.

Why did the prior national TR trial[3] study show significant benefit but 2 recent trials[71, 72] of activity-based therapy in-clinic did not? These divergent results might be due to the TR trial providing a higher therapy dose (42 hours in the TR trial[3] vs. 30[72]-32 hours[71]), a higher number of arm movements per session (1,031/session in the TR trial[3] vs ≤300/session[71]), and studying a population that was closer to the time of stroke (4.4 months post-stroke in the TR trial[3] vs. 12 months post-stroke[71]). Intensity of therapy may also be a factor, which might explain why both the prior national TR trial[3] and the CPASS trial[73] both showed substantial benefits.

**The rationale for investigating increased dopamine neurotransmission with intensive rehabilitation therapy**: Dopamine is a neurotransmitter that has a key role in learning, and plasticity[74-77], with increased dopamine associated with greater motor learning and motor cortex plasticity[78, 79] and decreased dopamine associated with impaired motor learning [80] and motor cortex plasticity [79]. Dopamine is also important to motivation[81], action learning[82], action selection[83], and in the control of voluntary exercise[84]. Dopamine is also a central component in the limbic reward system, and reward significantly influences long-term motor learning[85].

Given these well-established roles, dopaminergic drugs have also been investigated for poststroke recovery. One key study that motivates Aim 2 was a randomized, double-blind, placebo-controlled study of levodopa performed in patients who experienced a stroke 3 to 26 weeks prior, were admitted for inpatient rehabilitation, and lacked major depression[86]. A total of 53 patients were randomly assigned to 3 weeks of daily levodopa 100 mg (with carbidopa) or placebo coupled with physiotherapy. This study found that levodopa 100 mg/d combined with physical therapy was significantly better than placebo combined with physical therapy for improving arm and leg motor function at the end of the 3 weeks, measured using the Rivermead Motor Assessment. Motor gains were sustained or improved after an additional 3 weeks. No levodopa-related adverse events were reported.

A more recent study also found that levodopa was safe but, perhaps due to study design issues, did not find a benefit in motor recovery. The Dopamine Augmented Rehabilitation in Stroke trial[87] was a multicenter, randomized, double-blinded, placebo-controlled trial with pragmatic design features that examined 6-weeks of daily carbidopa/levodopa (25/100) given prior to rehabilitation therapy in 593 patients recruited 5-42 days post-stroke who could not walk independently. Levodopa was safe; the main safety finding was that vomiting after study drug administration occurred more often in the levodopa group as compared to the placebo group

(6% vs. 3%), a fact that is clearly noted in the informed consent form (ICF). Key concerns exist with the design of this study[88], concerns that limit interpretation of non-efficacy outcomes. First, the target population was not well defined, as this study enrolled patients with any deficit, of almost any severity, as long as gait was not independent; furthermore, the diagnosis of stroke was based entirely on clinical findings. Second, provision of concomitant physical therapy frequently did not follow study protocol. Third, the timing of pill ingestion relative to physical therapy was variable (e.g., the study drug was not taken per protocol in 45% of therapy sessions). Such details are critically important to trials of stroke recovery, and so perhaps the strongest message from this trial was that Sinemet 25/100 is safe early after stroke.

**The rationale for examining whether an intact corticospinal tract is needed to benefit from TR**: Aim 3 hypothesizes that patients with milder CST injury are more likely to achieve gains in arm function. Neural repair after stroke benefits from patient stratification[89], as patients with stroke are a heterogeneous population, with differing capacities to respond to rehabilitation therapy. Although several potential predictors of response to a restorative therapy in patients with subacute or chronic stroke have been identified[90-93], analysis[94] of data from patients receiving TR in the prior national trial[3] found that clinical measures provided limited prediction of TR-related arm motor gains. Following bivariate screening of 43 baseline clinical measures from eight categories, a multivariable linear regression model predicted only 17.6% of the variance in TR-related arm motor gains ($p<.004$). Other types of measurement beyond clinical data are needed to prospectively identify treatment responders.

Neuroimaging measures are excellent candidates for predicting benefit from rehabilitation after stroke. Indeed, such measures can be superior predictors compared to clinical measures. CST injury is the focus here because it is a common pathway for TR components: the mechanism of action for TR efficacy revolves around cortical plasticity from multiple circuits driving signals down the CST--and so greater CST injury would be expected to limit treatment-related behavioral gains. Five prior studies from the Cramer lab[70, 95-98] support this hypothesis, each finding that % CST injury was a significant predictor, explaining 17-33% of variance in arm motor recovery during receipt of a restorative therapy in subacute or chronic stroke. Importantly, in each of these studies, % CST injury was a better predictor than age, baseline behavioral status, and total infarct volume. For example, the largest of these studies[97], focused on patients in the subacute phase post-stroke, found that ≥75% CST injury had 91.7% positive predictive value that a patient would fail to achieve a gain on the Action Research Arm Test that reached or exceeded the minimal clinically important difference (MCID) of 5.7 points for this scale[99-104]. <u>These data suggest that treatment non-responders are common and can be accurately identified at baseline based on severity of CST injury</u>.

The method we use for measuring % CST injury involves [1] generating in healthy subjects a canonical CST emanating from primary motor cortex using diffusion tensor imaging (DTI) tractography, [2] outlining each patient's infarct on an anatomical MRI, and [3] overlapping each infarct on top of the canonical CST tract in MNI standard stereotaxic space. Ideally, we

would like to measure the percentage of axons in each CST that is injured by stroke, but MRI resolution does not permit this. Towards this approach, the CST is divided into 16 longitudinal subsections, aiming to model the trajectory of groups of axons. Each subsection is classified as injured or not; as with axons, a subsection need only be destroyed by stroke once along its length for it to be classified as injured.

**The rationale for examining whether dopamine genetics predicts benefit from TR and benefit from Sinemet**: Aim 3 hypothesizes that change in arm function will be highest in those with higher dopamine polygene scores. Dopaminergic drugs have long been studied towards the goal of improving outcome via enhanced brain plasticity after neural injury such as stroke. However, results to date have been inconsistent[105-107], with motor learning and plasticity improved by dopaminergic drugs in some studies[86, 108] but not in others[109-111]. Genetic measures might explain part of this variance and indeed might form a basis to personalize medicine by predicting which patients will be responders[112, 113]. Several prior studies suggest the utility of a dopamine polygene score based on 5 common and biologically active genetic polymorphisms. One study from my lab found that this polygene score can predict (a) motor learning, (b) motor cortex plasticity, and (c) their modulation with Sinemet 25/100[114]. Importantly, the predictive value of this dopamine polygene score was independently validated by Diaz Heijtz at the Karolinska Institutet[115] in a study of intensive arm motor therapy provided to hemiparetic children with cerebral palsy. Separately, my lab also found that this polygene score predicted depression scores in healthy subjects and in subjects with major depression[116]. MacDonald et al at University of Auckland found that the same polygene score was able to predict extent of impulse control and whether these symptoms responded favorably to a dopamine agonist drug[117]. For these reasons, this polygene score will be tested as a predictor of treatment effect in each patient group.

**A pilot study of TR in patients with chronic stroke**[13] was an extension of the Cramer lab's longstanding experience studying game-based robotic arm motor therapy for patients with stroke[46, 96, 118-127]. A pilot study transferred these and other games to a TR system, then tested it in 12 patients with chronic (>6 months post-onset) stroke. Each patient received 4 weeks of home-based, therapist-supervised TR targeting arm motor deficits. We found that

- Patients were highly compliant (97.9% of assigned days) and rated the system favorably;
- Therapists in the clinic were able to remotely review patient performances and revise therapy;
- Videoconferences supported regular communication between the patient and treatment team;
- Arm motor status improved significantly based on the FMA-UE;

- Daily stroke education significantly increased secondary stroke prevention knowledge;
- Screening for depression using telehealth methods was accurate;
- No computer skills were needed, as computer literacy was not related to usage or treatment gains; and
- With 60 min/day of TR in this pilot study, patients averaged 879 arm repetitions/day.

These results support the feasibility and potential utility of this home-based program for improving outcomes after stroke.

**A multisite, randomized, assessor-blinded trial of TR**: Subsequently, my lab led an 11-site national trial[3] in the NIH StrokeNet clinical trials network. The primary aim was to determine whether treatment targeting arm movement delivered via a home-based TR system has comparable efficacy with dose-matched, intensity-matched therapy delivered in a traditional in-clinic setting. A randomized, assessor-blinded, non-inferiority design was employed. Entry criteria included stroke with onset 4-36 weeks prior and arm motor deficits (defined as UE-FM score of 22-56 of 66). Patients were randomized to TR therapy in the home or therapy at an outpatient clinic. All enrollees were assigned 36 sessions (70 minutes each) of arm motor therapy plus stroke education. Therapy intensity, duration, and frequency were matched across groups.

Main results of the multisite, randomized, assessor-blinded trial: The 124 enrollees had baseline FMA-UE score of 43±8 (mean±SD) points (maximum score, 66 points; higher scores are better), and were enrolled 18.7±8.9 weeks post-stroke. Compliance was 98.3% in the TR group and 93.4% in the in-clinic group. Change in FMA-UE score from baseline to 1-month post-therapy (the primary endpoint) was 8.4±7.0 points for the in-clinic group vs. 7.9±6.7 points in the TR group. The covariate-adjusted FMA-UE score change was 0.06 (95% CI -2.14, 2.26) points higher in the TR group (p=0.959). The non-inferiority margin fell outside this 95% CI, which indicates that TR is not inferior to dose-matched therapy provided in-clinic. Motor gains associated with TR therapy remained significant whether patients were enrolled early (<90 days) or late (>90 days) post-stroke. Gains were also significant when examining change in the Box & Blocks Test (BBT) score, a measure of arm function (activities limitations). Stroke Knowledge scores also increased significantly (p<0.001). A post hoc analysis found that TR was associated with improved global function (mRS score) in 39.5% of patients beginning therapy after day 90[14], a time when functional recovery generally stabilizes[128].

The number of arm movement repetitions over 36 TR treatment sessions was calculated in a convenience sample. With 70 min/day of TR, patients averaged 1,031 arm repetitions/day, 33-times higher than the amount of arm movement provided during standard of care[4].

In sum, a 6-week course of daily home-based TR supervised by a licensed OT or PT was safe, rated favorably by subjects, associated with excellent treatment compliance, and produced substantial gains in arm function that were not inferior to a dose-matched.

**A pilot study of TR for patients at an early timepoint after stroke**: Most recently, we have performed a pilot study of TR in patients who were in the early weeks post-stroke. Patients were enrolled during admission to an IRF. Thus far we have enrolled 11 patients at California Rehabilitation Institute (Cal Rehab), each of whom had recent stroke and arm paresis. Enrollees received the 6-week TR program as described here, using the very same software and hardware described here. Each was assessed immediately before and after the 6-week course of TR.

Baseline features include age 62.5±14.4 (mean  SD), median of 21 days post-stroke at time of first TR session, median of 6 TR sessions provided while the patient was still admitted to the IRF, FMA-UE score 33.2±5.4, and BBT score 7.6±9.6.

Behavioral gains at the end of 6-weeks of TR included a mean increase in FMA-UE score of 22.6±10.3 points; in BBT score, 26±8.4. These behavioral gains are strongly driven by spontaneous post-stroke recovery and it is difficult to understand which component may be attributable to TR effects, but these gains are nonetheless quite favorable.

In terms of safety, there have been 9 adverse events (AEs), 2 of which were considered possibly or probably related to study participation. Both were non-serious. [1] one patient with hemianopsia felt nausea while using his own physician-prescribed prism glasses during TR, which was relieved by increasing breaks between TR activities and providing the option for anti-nausea medication; and [2] one patient who was being treated for depression reported feeling demotivated and depressed when asked to score anxiety and depression scales online, which was addressed by removing these assessments from his future sessions.

This study establishes the feasibility and safety of providing intensive TR to patients with severe motor deficits very early after stroke.

**In sum**, we now propose to evaluate this intervention in a larger cohort of patients early after stroke, testing whether TR is better than an inactive control, and examining whether introducing levodopa enhances the benefits expected from daily intensive arm motor therapy delivered via TR.

## Schedule of Events

The table below provides an overview of the schedule of assessments and other tasks that will be completed by subjects in all groups.

| ASSESSMENT/TASK | ELIGIBILITY SCREENING | VISIT 1 | VISIT 2 | TR Week 1^ | TR Week 2^ | TR Week 3^ | TR Week 4^ | TR Week 5^ | TR Week 6^ | VISIT 3 | VISIT 4 | VISIT 5^^ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **TR Session #** | | | | *1-6* | *7-12* | *13-18* | *19-24* | *25-30* | *31-36* | | | |
| **Study Overview** | X | | | | | | | | | | | |
| **Informed Consent & HIPAA** | X | | | | | | | | | | | |
| **Research Participant's Bill of Rights (handout)** | X | | | | | | | | | | | |
| **Past Medical History Demographic/Contact Information** | | | | | | | | | | | | |
| **Interval Medical History** | | | X | X | X | X | X | X | X | X | X | X |
| **Adverse Events** | | | X | X | X | X | X | X | X | X | X | X |
| **Action Research Arm Test (ARAT)** | X Must be <32 | | | | | | | | | X | X | X |
| **AROM shoulder and elbow flexion OR** *able to use at least 3 different input devices* | X At least ≥45° | | | | | | | | | | | |
| **Box and Blocks Test (BBT)[α] OR Wrist extension and finger flexion[β]** ***Gravity eliminated*** | X BBT must be ≥1 | | | | | | | | | X | X | X |
| 10-s and 3-block BBT | X | | | | | | | | | X | X | X |
| **3 Rehab Practice Tasks** | X Must pass all | | | | | | | | | | | |
| **Center for Epidemiologic Studies Depression Scale – 20 item (CES-D)[Ω]** | X Must be ≤24 | | | | | | | | | | | |
| **Center for Epidemiologic Studies Short Depression Scale – 10 item (CESD-R-10)[Ω]** | | | | | | X | | | X | | | |
| **Montreal Cognitive Assessment (MoCA)** | X Must be >22 | | | | | | | | | | | |
| **Visual Acuity Screen** | X Must be ≥20/50 in one eye | | | | | | | | | | | |
| **Trail Making Test: Part A only** | X | | | | | | | | | | | |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Must be >14 | | | | | | | | | | | |
| **Eligibility Checklist** | | X | | | | | | | | | | |
| **Behavioral Contract** | X | | | | | | | | | | | |
| **Randomization** | X | | | | | | | | | | | |
| **Pharmacy – Fill Prescription** | X | | | | | | | | | | | |
| **MRI Safety Screening Questionnaire** | X | | | | | | | | | | | |
| **Fugl-Meyer Motor Assessment – Upper Extremity (FMA-UE)** | | X | | | | | | | | X | X | X |
| **Modified Rankin Scale (mRS)**[μ] | | X | | | | | | | | X | X | X |
| **Shoulder Abduction Finger Extension (SAFE) Score** | | X | | | | | | | | | | |
| **Handedness Inventory** | | X | | | | | | | | | | |
| **Star Cancellation Test (SCT)** | | X | | | | | | | | | | |
| **The Language Screening Test (LAST)** | | X | | | | | | | | | | |
| **Nine Hole Peg Test (NHPT)** | | X | | | | | | | | X | X | X |
| **Stroke Impact Scale (SIS) – ADL subsection** | | | | | X* | | | | | X | X | X |
| **SIS – Hand subsection** | | | | | X* | | | | | X | X | X |
| **Modified Ashworth Scale Pecs & Biceps** | | X | | | | | | | | | | |
| **Review of TR System** | | X | | | | | | | | | | |
| **Reaction Time Test** | | X | | | | $X^1$ | | | $X^2$ | | | |
| **Optimization in Primary and Secondary Control (OPS) Scale** | | X | | | | X | | | X | | | |
| **Physical Activity Enjoyment Scale (PACES)** | | X | | | | $X^{\Sigma}$ | | | $X^{\Sigma}$ | | | |
| **Screening Q re: Restless Legs Syndrome** | | X | | | $X^{2*}$ | | | | | | | |
| **Genetic Testing** | | X | | | | | | | | | | |
| **TR System Delivery** | | | | X (TR Group) | | | | | | | X (UC Group) | |
| **Call UC Subjects (reminder re: participation and logging therapy hours, inquire about adverse events)** | | | | Every 1-2 weeks | | | | | | | | |
| **MRI**[+] | | | X | | | | | | | | | |
| **Shoulder Pain** | | | | Daily (Start and End of Therapy) | | | | | | | | |
| **Fatigue** | | | | Daily (Start and End of Therapy) | | | | | | | | |
| **Daily Motor Assessment** | | | | Daily (Start of Therapy) | | | | | | | | |
| **Finger Tap Assessment** | | | | Daily (Start of Therapy) | | | | | | | | |

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| **Degree of Perceived Effort** | | | | Daily (End of Therapy) | | | | | | | | |
| **Stroke Education Quiz** | | | | X | | | | | X | | | |
| **Stroke Education** | | | | | Daily | | | | | | | |
| **Functional Module** | | | | | | | | X** | X** | | | |
| **Euro-QoL Visual Analog Scale (VAS)** | | | | X | | | | | X | | | |
| **General Anxiety Disorder 7-item Scale (GAD-7)** | | | | | X | | | | | | | |
| **Medical Outcomes Study (MOS) Social Support Survey (SSS)** | | | | | | X | | | | | | |
| **Guess Medication** | | | | | | X[2] | | | | | | |
| **Brief Resilience Scale** | | | | | | | X | | | | | |
| **Functional Training Module** | | | | | | | | X | X | | | |
| **Patient Satisfaction with TR Survey** | | | | | | | | | X | | | |
| **TR System Pick-up** | | | | | | | | | X (TR group) | | | X (UC Group) |

^ Only patients in the TR groups will be undergoing TR training for 6 weeks

α Splint permitted for use during BBT for study eligibility only

β Patient must show visible flicker (trace movement) in all 4 movements tested, if BBT not ≥1

Ω Tally score on day assessment is completed, and contact the patient's care team if the score is high, per SOP guidance

μ At Visit 1, complete pre-stroke and current mRS; current mRS for all other visits

∑ additional question to be asked post-assessment (refer to CRF for details)

*completed within 5 days after DC home (SIS) or during week 2 (SIS or Restless Leg Screening Q); for UC subjects, the SIS ADL and hand and Restless Leg Screening question will be completed during Week 2, after randomization

[1]completed during start of week

[2]completed during last supervised session of week

+ timing of the MRI may be modified per PI judgment

**schedule 5-10 minutes on supervised days only, to observe practice of functional task related to goal

^^ Visit 5 only applies to participants in the UC group who choose to participate in TR training after their initial study participant has ended

# Screening, Recruitment, and Enrollment

## Recruitment:

Patients will be recruited from two main sources. First, patients with a recent stroke admitted to Cal Rehab, an inpatient rehabilitation facility (IRF) in Los Angeles, CA, will be screened and when appropriate offered study enrollment and a Screening Visit. Second, patients with a recent stroke who have been discharged home then referred to the study will be invited to Cal Rehab for pre-screening and when appropriate study enrollment and a Screening Visit. These referrals may come from outside sites.

Research activities at Cedars-Sinai: One of these referral sites will be Cedars Sinai, who will refer patients as above. Cedars personnel will also assist with (1) reviewing and refining study procedures, and (2) data analysis and results reporting.

## Pre-screening:

Pre-screening will occur before the patient is asked to sign consent. For patients admitted to Cal Rehab, pre-screening will consist of review of the medical record plus a very brief pre-screening exam that aims to identify severe paralysis, severe cognitive or language deficits, or other major abnormalities that clearly indicate that a patient is not eligible for the study. For patients referred to the study from the community, pre-screening will occur during the initial phone call and during a very brief pre-screening exam performed after the patient arrives at Cal Rehab. Patients considered to have a reasonable likelihood of study eligibility will be offered study enrollment. The Screening Visit will then proceed, and this takes place at Cal Rehab.

## Enrollment

The initial steps of study enrollment are as follows:

- Provide the patient with an overview of the study and the study timeline
- Have the patient sign the ICF and the Health Insurance Portability and Accountability Act (HIPAA) Research Authorization for Release of Protected Health Information (PHI)
- Provide the patient with a copy of the Research Participant's Bill of Rights
- Gather demographic data, medical history, and contact information, from the patient, from a subsequently obtained copy of medical records, and when possible from the electronic health record
- Complete baseline screening measures to confirm study eligibility, including:
    - **Action Research Arm Test (ARAT)**
    - **Box and Blocks Test (BBT)**

**If unable to complete BBT, will examine wrist extension and finger flexion for a visible flicker** (at least trace contraction must be present for both movements)

- **Examine range of motion against gravity in the paretic shoulder and elbow**
- **3 Rehabilitation Practice Tasks**
- **Center for Epidemiologic Studies Depression Scale** (CES-D, 10 questions)
- **Montreal Cognitive Assessment** (MoCA)
- **Trail Making Test** (TMT)**: Part A**
- **Visual Acuity Screen**

- Complete the Eligibility Checklist, which evaluates whether the patient fully meets inclusion and exclusion criteria
- If the patient is an inpatient at Cal Rehab, enter a research progress note into the electronic health record (Epic)

The Screening Visit may be broken into more than one session, as needed.

If the patient meets all of the eligibility criteria and is amenable to study participation, they will given a Visit 1 follow-up appointment, ideally on the next day.

## Inclusion and Exclusion Criteria

Below is a list of the study inclusion and exclusion criteria. The Eligibility Screening packet includes an eligibility checklist, which must be completed to confirm whether a patient is eligible or ineligible for participation.

### INCLUSION CRITERIA

1. Age 18 years or older
2. Stroke that has been radiologically verified and has time of onset 30 days or less from the time of randomization
3. ARAT score of <32 (out of 57) at Visit 1
4. At Visit 1, either
    a. BBT score with affected arm is at least 1 block in 60 seconds OR
    b. There is a visible flicker in each of the following movements with gravity eliminated: wrist extension and finger flexion

5. At Visit 1, either
    a. The range of motion against gravity must be ≥45 degrees in both the paretic shoulder and elbow OR
    b. the patient must be able to use at least 3 different telerehab system input devices
6. Informed consent and behavioral contract signed by the subject (i.e., no surrogate consent)

## EXCLUSION CRITERIA

1. A major, active, coexistent neurological or psychiatric disease (e.g., alcoholism or dementia)
2. Major medical disorder that reduces subject's ability to comply with study procedures
3. Severe depression, defined as CES-D score >24 at screening visit
4. Significant cognitive impairment, defined as presence of either
    a. Montreal Cognitive Assessment (MoCA) score <22 OR
    b. Trail Making Test: Part A score ≤14
    c. Note that lower scores may be permitted if due to aphasia and if the patient is specifically allowed by Dr. Cramer
5. Deficits in communication that interfere with reasonable study participation
6. Lacking visual acuity, with or without corrective lens, of 20/50 or better in at least one eye
7. Life expectancy <6 months
8. Pregnant
9. Botox to arms, legs or trunk in the preceding 4 months, or expectation that Botox will be administered to the arm, leg or trunk within 3 months of study enrollment
10. Unable to successfully perform all 3 rehabilitation exercise test examples
11. Unable or unwilling to perform study procedures/therapy or attend study visits, or expectation of noncompliance with study procedures/therapy
12. Non-English or non-Spanish speaking, such that subject does not speak either language sufficiently to comply with study procedures
13. Isolation due to active COVID-19
14. Any contraindication to L-Dopa:

a. Patient is currently taking a monoamine oxidase inhibitor; if the patient took such a drug in the past, it must be discontinued at least two weeks prior to study enrollment
b. Known hypersensitivity to any component of Sinemet
c. Narrow-angle glaucoma; if wide-angle glaucoma is present, the patient can only be enrolled with explicit written approval from their ophthalmologist
d. History of melanoma or suspected melanoma
e. Patient is currently taking phenytoin, papaverine, isoniazid, or a dopamine D2 receptor antagonist (such as a phenothiazine, butyrophenone, or risperidone)
f. Currently taking a direct dopaminergic agonist

15. Expectation that subject will not have single domicile address during 6 weeks of therapy that has either Verizon wireless reception or a home WiFi network and that has space for TR system, and is within 30 miles of Cal Rehab

Any of the above entry/exclusion criteria can be waived by Dr. Cramer.

In addition, we will enroll up to 3 patients in a beta study, in which Inclusion criteria 2 and 3 are waived.

# Visit 1

Visit 1 will occur at Cal Rehab. Seven key events occur at Visit 1:

1. Baseline assessments are completed
2. Blood is drawn for genetic testing
3. MRI Screen
4. The patient is randomized
5. Dispense study medication (at or shortly after Visit 1)
6. The patient is asked to sign the behavioral contract
7. The TR system is introduced.

## Baseline Assessments

Additional assessments will be completed during Visit 1 in order to more fully characterize the patient's functional status at baseline:

- **Fugl-Meyer Arm Motor Assessment for the upper extremity (FMA-UE**)
- **Modified Rankin Scale** (mRS), scoring both
  - pre-stroke mRS
  - current mRS
- **Shoulder Abduction Finger Extension** (SAFE) **Score**
- **Handedness Inventory** (pre-stroke)
- **Star Cancellation Test** (SCT)
- **The Language Screening Test** (LAST)
- **Nine Hole Peg Test** (NHPT)
- **Optimization in Primary and Secondary Control** (OPS) **Scale**
- **Physical Activity Enjoyment Scale** (PACES)
- **Screening question for Restless Legs Syndrome**
- **Reaction Time Test**
- **Modified Ashworth Scale** (mAS)
  - paretic pectoralis major
  - paretic biceps brachii

All Visit 1 assessments are available in a single "Visit 1" packet, located in the lab's Box folder. Details regarding administration of each assessment is found within individual CRFs. The Visit 1 folder on Box also includes a handout for TR input devices, which can be given to patients for reference. Visit 1 may be broken into more than one session, as needed.

After all assessments have been completed, provide an overview of how to access and use the TR system for daily arm motor training.

Note that all study visits may be broken into more than one visit to the lab for any patient who requests this (e.g., due to time constraints).

## Genetic Testing

For genetic testing, DNA and genotyping data will be collected from patients under the protocol described in IRB#10-001577 using a separate consent process. Two 4 mL tubes of blood will be drawn into lavender top (EDTA) collection vials and taken to the genetics lab at UCLA for processing, to test the genotype-based biomarker hypothesis (Aim 3).

## MRI Screen

A standard MRI screen will be conducted at Visit 1. Patients eligible for MRI will proceed to Visit 2 for the MRI scan, whereas those who are not eligible for an MRI scan may still be eligible for study inclusion per Dr. Cramer. The timing of the MRI may be modified per PI judgment.

## Randomize the patient

Using a web-based randomization procedure, the patient will be randomized into one of three treatment groups:

- **TR + Sinemet:** Patients in this group will receive 36 therapy sessions targeting arm motor function starting as soon as possible after randomization (target is next day). This therapy is structured as 6 weeks of TR, 6x/week, for 6 weeks. Up to 8 weeks are permitted to make up for lost sessions to achieve 36 sessions in which >50% of assigned minutes are completed by the patient. For the first 18 sessions (approximately the first 3 weeks), the patient will take their study pill (Sinemet 25/100) 1-2 hours after breakfast or lunch, then 1 hour later begin their 70-min TR session. TR+Sinemet is in addition to UC (i.e., the patient is to continue all therapies and medication provided as part of standard medical care).
- **TR + placebo:** Patients in this group will receive 36 therapy sessions targeting arm motor function starting as soon as possible after randomization (target is next day). This therapy is structured as 6 weeks of TR, 6x/week, for 6 weeks. Up to 8 weeks are

permitted to make up for lost sessions to achieve 36 sessions in which >50% of assigned minutes are completed by the patient. For the first 18 sessions (approximately the first 3 weeks), the patient will take their study pill (placebo) 1-2 hours after breakfast or lunch, then 1 hour later begin their 70-min TR session. TR+placebo is in addition to UC (i.e., the patient is to continue all therapies and medication provided as part of standard medical care).

- **Usual care (UC):** Patients in this group will not receive TR or a blister pack of study pills. Instead, each will receive UC (i.e., will continue all therapies and medication provided as part of standard medical care). In order to maximize participant retention, patients in this group will be offered a 6-week course of TR after Visit 4 (i.e., 5-6 months after stroke). At the end of their TR therapy, at the time that their TR system is picked up from their home, the therapist will perform ARAT, FMA-UE, BBT, NHPT, and mRS in the patient's home.

## Dispense Study Medication

Study medication will be dispensed at Visit 1, or shortly after. Patients randomized to the TR+Sinemet and the TR+placebo groups will be given a blister pack of 18 pills with instructions to take one pill an hour after breakfast or lunch 6 days/week for the first 18 sessions (approximately the first 3 weeks). TR will begin 1 hour after pill ingestion. Patients will be given apple sauce to take with their pill as needed, following dysphagia restriction guidelines, to mitigate concerns for potential nausea. As needed, patients may also be provided with an antacid drug. Patients in the UC group will not be given a blister pack of study pills or apple sauce.

The UCLA Pharmacy will generate the two types of study pills (i.e., Sinemet 25/100 and placebo). These two pills will be indistinguishable internally and externally (i.e., the internal powder will be the same color, and the external over-encapsulation will be identical), across both pill types. Pills will be organized into an 18-pill blister pack.

In patients with stroke, oral Sinemet 25/100 once/day is not associated with increased risk or with decreased acceptability of risks[86, 87] For this reason, the current study does not need to be conducted under an investigational new drug application to the FDA.

## Behavioral Contract

Patients sign a group-specific behavioral contract[3, 12]. For patients in the two TR groups, this contract describes the patient's commitment to engaging in study-assigned therapy, includes a personal goal, outlines a plan to incorporate the paretic UE into daily life, and states the time of day when TR will generally begin.

## TR System Overview

Patients will be participating in daily (6 days/week) TR training over the course of 6 weeks (up to 8 weeks is permitted to complete 36 sessions). If an enrollee is an inpatient at Cal Rehab at the time of enrollment, guidance for use of the TR system will be at the end of Visit 1 and at subsequent inpatient TR sessions. If the enrollee is an outpatient referred into the study, guidance for TR use will occur at Visit 1 and at the time that the TR system is delivered to the patient's home. TR guidance will provide an understanding of the general TR layout, the nature of the functional games and exercises used for arm training, other modules such as education and assessment, how to respond to instructions (which are presented verbally and non-verbally as a TR system feature), and how to use each TR input device.

# Visit 2

Visit 2 will be conducted on the UCLA campus. At Visit 2, the patient will undergo an MRI scan of the brain to acquire structural and functional brain images. Pulse sequences will include T1-weighted, T2-weighted, resting state BOLD T2*, and diffusion tensor imaging. These data will be used to test MRI-based biomarker hypotheses (Aim 3). At this visit, the patient will also be asked about any interval medical history and AEs.

Note: The timing of the MRI may be modified per PI judgment.

# TR System Home Delivery

The TR system should be delivered to the patient's home (a) as soon as possible after discharge from Cal Rehab, for patients enrolled while admitted to Cal Rehab, and (b) as soon as possible after Visit 2, for patients referred into the study. Two research staff members should be present for all home visits, when possible.

In addition to setting up the TR equipment and connecting it to WiFi, patients should be given a quick overview of the TR system, confirm the patient's study schedule, and ensure a caregiver will be available to assist with transfers and supervision if needed. The patient's own home WiFi should be used to connect the TR system to the internet, if possible, else a study-provided wireless modem will be furnished and employed for this purpose, as we have successfully done previously[129].

# TR Therapy

## The telerehabilitation intervention

**Summary**: Patients are assigned 70 minutes of telerehabilitation (TR) therapy each day, 6 days/week, for 6 weeks, targeting the paretic UE. Functional games and exercises comprise 65 of these daily minutes, and 5 minutes/day is spent on stroke education (which requires targeted arm movement).

Therapy must begin within 7 days of randomization. The first TR session will be a supervised session, whether in-person or via videoconference.

TR is delivered over 36 sessions, each 70-minutes in duration. Of these, 18 sessions are supervised by a licensed OT or PT; for patients receiving TR while admitted to Cal Rehab, the therapist may be in the same room as the patient or communicate via videoconference, and for patients who are at home, the therapist is present via videoconference. The other 18 sessions are unsupervised (i.e., no OT or PT is present at any time during the session; for inpatients at Cal Rehab, the therapist can sit near the patient, with minimal interaction, at the therapist's judgment). Ideally, a given patient will work with the same therapist[1] for the entire 6 weeks. To accommodate possible external events (e.g., illness or family reasons), patients are permitted up to 8 weeks to complete these 36 treatment sessions. **In the prior national trial[3], the FDA determined (Q140628) that the investigation using an earlier generation of the same device was a non-significant risk device study**. **The FDA made the same determination (Q212693) for the current study.** When possible, patients begin TR each day at the time indicated in the behavioral contract. Patients are free to pause between games and activities, as needed. Patients are also instructed to perform all UC that is provided to them–enrollment in this TR study does not interfere with any treatment provided as part of standard of care. A session is considered completed when the patient has completed >50% of the assigned 70 minutes by midnight. After the 36 treatment sessions are completed, or if that does not happen then at the end of 8 weeks, the team retrieves the TR system from the patient's home.

The TR treatment approach was based in part on an UE task-specific training manual[130] and Accelerated Skill Acquisition Program[72], building on games developed as part of previous studies from the Cramer lab that used a game-based approach to therapy after stroke, in the context of robotics[46, 96, 118-127].

Feedback to patients is a core feature and comes from two sources. First, therapists give feedback on supervised days based on their observations during videoconference plus their review of electronic data such as prior days' device usage and scores on functional games. Second, the TR system gives patients feedback (e.g., during a game such as whether a game target was hit or not, and after a game when current/past scores game scores are presented).

In this way, incorporation of feedback in the current TR system directly builds on OPTIMAL theory[131]. Feedback provided by the TR system during gameplay and at the end of each game emphasizes enhanced expectancy and reward during gameplay. Positive feedback is also provided by the therapist during supervised sessions. Autonomy is promoted by using a home-based treatment approach and by having half of treatment days be unsupervised (i.e., there is no interaction with a therapist). External focus on attention is facilitated by therapist feedback and by the approach to gameplay.

The active ingredients of TR within the RTSS [65, 66] framework are summarized above, which emphasizes that playing the TR functional games is not simply rote movement repetition but instead targets specific brain circuits (memory, attention, somatosensory, visuomotor, and cognitive circuits) that drive motor output. Specific dosing parameter goals and dose progression strategies are outlined for treatment therapists.

## Therapist-facing software

We developed a therapist-facing web portal that treatment therapists use for treatment planning and patient monitoring. All treatment is generated and supervised by a licensed OT or PT. Therapists use a graphical interface to drag treatment elements (functional games, exercises, and stroke education) into a 70-min planner for each day's session; they then adjust the challenge level (games) and the duration (games and exercises) of each.

**Videoconferences**: For the supervised sessions that occur for patients who are living in their home, the treatment therapist joins the patient for 60 minutes of their session using HIPAA-compliant software (VSee; Sunnyvale, CA). Supervised sessions that occur while a patient is still admitted to Cal Rehab may have the therapist join the patient via VSee or live in the patient's room, per the therapist's judgment. During supervised sessions, therapists monitor therapy and provide patients with real-time positive feedback, answer questions, perform assessments, review treatment plans, and provide encouragement. Therapists also discuss how UE movements practiced during TR can be extended to become part of activity in the home. Any AEs and serious adverse event (SAEs) are reviewed. Note that 9.7% of patients receiving TR in the national trial[3] had shoulder pain, and all patients could be helped by their therapist remotely, without pausing TR therapy. Therapists write an electronic clinic note after each videoconference, as standard good clinical practice.

The same therapist-facing web portal allows therapists to review, at any time, from any secure location:

Usage statistics: For games and for the stroke education module, we use the TR system's sensors--every game click, tap, squeeze, or shot is sent to the lab server in real time.

Performance data: We provide therapists with concise graphic readouts of scores on each game, over time. In this way, therapists can monitor patient compliance and performance, and

then use their professional judgment to modify game/exercise choices and difficulty levels accordingly, at any time.

## Patient-facing software

Each of the 36 TR sessions is 70 min and includes 65 min/day of functional games and exercises, plus 5 min/day of stroke education–all of which require arm movements.

(1) Arm exercises. A total of 114 UE exercises are available, each 1-5 min long and consisting of a video showing the assigned movement. Therapists may choose to demonstrate some of the exercises during videoconferences on supervised days. In addition, therapists have the option to incorporate standard exercise equipment (e.g., Theraband) that is also provided to patients at the time the TR system is delivered to the home and that can be incorporated into assigned exercises.

(2) Functional training through games. There are 25 functional games, each 1-5 min long. These stress motor control features (e.g., varying movement speed, range of motion, squeeze strength, pinch strength, target size and features, extent of visuomotor tracking, memory demand, unilateral vs. bilateral movement, or level of cognitive demand). Features are selected and adjusted by the therapist, e.g., during the whack-a-mole game, higher difficulty level means a broader area where targets can appear and less time to hit the target to score points. Therapists also select which of the 11 input devices the patient will use for game play, based on UE motor status, e.g., vertical position of the flying bird in the flappy-bird game can be played using the grip force cylinder, pinch force cube, or trackpad. Feedback is provided during the game (e.g., when targets are hit), at the end of each game (today's score along with prior scores), and at the end of the day (graphs of progress over time).

(3) Five minutes/day of stroke education. The education content targets 5 categories (Stroke Risk Factors, Stroke Prevention, Effects of Stroke, Diet, and Exercise). During unsupervised sessions, patients answer multiple-choice questions, delivered via a video Jeopardy game format, an approach known to foster learning[132, 133], and then receive feedback on their answers. Patients must make targeted arm movements to play the Stroke Jeopardy game. These 5 min/day significantly increase patient knowledge on stroke-related topics[3, 13]. A Stroke Knowledge Exam is administered through the TR system during the first and the last week, to measure knowledge gains in these five categories.

To begin the day's TR session, the subject hits a large green tabletop button. After each game/exercise is completed, the same green button is hit again to start subsequent games/exercises, an approach that provides patients with the freedom to take a break as needed. Unsupervised sessions have the same treatment content as supervised sessions but without any therapist contact.

All patient interactions with the TR system incorporate both verbal and non-verbal instructions. Instructions are simple and use a large-font and large symbols.

## TR hardware

The telerehabilitation system hardware consists of an internet-enabled computer with table, chair, and 11 gaming input devices–but no keyboard, as no computer operations are required by subjects and no computer literacy is needed for high compliance or for arm improvement. The 11 devices are large tabletop buttons, small tabletop buttons, a trackball mouse, rotating shuttle wheel, trackpad, grip force cylinder, pinch force cube, a Wiimote equivalent inside gaming pistol, a tracking wand, joystick, and an accelerometer attached to an easy grip.

The console itself is created using a 22cm x 22cm Ikea “Lack” side table, which is made of particle board. The legs aren’t used. The top has its bottom and internal honeycomb structure removed, and holes are cut into the top and sides for all the components. Drawer handles are attached for easier handling and transport.

Gaming input devices are used to move through assignments, drive game play, and enable assessments and education. Some of these devices are connected directly to the top of the table. These are [1] four 100mm arcade buttons with internal LEDs, [2] a DIY arcade kit that includes ten 30mm JAMMA/MAME style arcade push buttons and joystick, [3] a 4.5cm PS/2 Trackball mouse, [4] a 360-degree Rotary Encoder Digital Potentiometer with Push Button, and [5] a USB trackpad. All of these components are available through Amazon.com except the USB trackpad, which we purchased directly from an original equipment manufacturer vendor. The Potentiometer is fitted with a ThunderStick GRS Spinner Knob that can be swapped out with custom 3D printed tops that require various types of finger grips.

Other gaming input devices are connected to the side of the table via a plug: [1] a force sensor built using a 20kg Load Cell Sensor, [2] a pinch sensor using Interlink model 402 Force-Resistive Sensor, [3] a pistol built using an RB-Dfr-553 IR Tracker, [4] a wand that uses another RB-Dfr-553 IR Tracker, and [5] a BNO055 sensor which is a 9 Degree of Freedom IMU. All the housings for these devices are 3d printed in the lab. For sensors that require 2 wires, we use 3.5mm audio jack connectors and lightweight headphone cables. For sensors that require 3 or more wires, we use RJ45 Keystone adapters and Monoprice SlimRun ethernet cables to minimize the weight. The pistol is made up of a commercially available Wii Remote gun shell, a 3D printed adapter to fit the IR tracker, and splicing of the Wii port connector to an RJ45 connector to make it detachable.

Internally, all components are hooked up to 2 Arduino Mega microcontrollers. The first controller handles all the button inputs and has had its firmware flashed to convert it into a standard USB human interface device keyboard; in this way, each button press translates to a standard keystroke viewable on any computer. The second microcontroller handles the LED outputs as well as other digital and analog sensors, and it communicates directly with a

controlling PC using a serial connection. To wire all the components together in a clean manner, a circuit board was designed and printed. We used JLCPCB.com for this service. The circuit board allows for direct mounting of all components since we can solder on screw terminals, JST pin connectors, resisters, and header pins. Using this approach makes things removable and reduces the number of wires required to assemble everything. Several of the sensors use an I2C connection, so we included an I2C Multiplexer into the circuit, as well as a HX711 AD Weighing Module that's required for the load cell to function correctly.

The final component is a standard USB hub, which is mounted internally as well, but accessible from the outside through a cutout. We used a 7 port USB 2.0 hub. Both Arduinos and the trackpad connect to the hub, which has a power connector as well as a USB connector that must be connected to a computer. Thin plywood bought from Home Depot and cut to match the Ikea Lack Table is screwed onto the bottom of the console to seal it. A barrel jack connector on the side of the table that is connected to the Arduino 5V output allows us to power the external 940nm IR LEDs necessary for the IR trackers to work.

The console connects via USB to a computer, such as a Lenovo B50 All-In-One PC, which runs our custom TR program, Teamviewer, and VSee. These PCs run Windows 10 Pro and have i5-4460T Processors, 8GB of RAM, and upgraded with Samsung 500GB SSD drives.  Video chat uses the internal webcam. Three 940nm IR LEDs are attached to the front for tracking.

# TR-based assessments

Several behavioral assessments will be completed remotely during Weeks 1 to 6 using the TR system. These will be scored during supervised sessions, while the therapist is in the videoconference. In addition, once each week, the therapist will ask the patient about interval medical history and AEs.

## Daily assessments performed using the TR system

- Daily motor assessment (Whack-A-Mole game using the hand, scores # targets hit in 90 seconds)
- Daily finger tap assessment (scores # index finger taps on small button in 10 sec, reported in Hz)
- Daily shoulder pain scoring– uses Visual Analog Scale (VAS)
- Daily fatigue scoring– uses VAS
- Degree of Perceived Effort – uses VAS

## Week 1 additional assessments

- EuroQoL Visual Analog Scale (EQ VAS)
- Stroke Education Quiz (5 questions/day x 6 days)
- The patient will be asked about interval medical history and AEs

## Week 2 additional assessments

- Stroke impact scale – ADL and Hand subsections (administered during week 2 or within 5 days of DC home)
- General Anxiety Disorder 7-item (GAD-7) Scale
- Screening question for possible diagnosis of Restless Legs Syndrome
- The patient will be asked about interval medical history and AEs

## Week 3 additional assessments

- Reaction Time Test
- Medical Outcomes Study Social Support Survey (MOS-SSS)
- Center for Epidemiologic Studies Short Depression Scale (CESD-R-10)
- OPS and PACES
- Guess Medication (Patients asked which pill they think they were taking each day.)
- The patient will be asked about interval medical history and AEs

## Week 4 additional assessments

- Brief Resilience Scale (BRS)
- The patient will be asked about interval medical history and AEs

## Week 5 additional assessments

- The patient will be asked about interval medical history and AEs

## Week 6: additional assessments

- Stroke Education Quiz (5 questions/day x 6 days)
- Reaction Time Test
- EQ VAS
- CESD-R-10
- OPS and PACES

- Patient Satisfaction with Telerehabilitation Survey
- The patient will be asked about interval medical history and AEs

# Visit 3 (End of Treatment)

The end-of-treatment visit will generally be conducted at Cal Rehab, but accommodations for home assessment will be made as needed.

If the testing occurs in the patient's home, two research staff members should be present, when possible: one person to conduct final assessments with the patient and the other to deconstruct and clean equipment for transport back to the lab.

## Assessments

*Several standardized assessments will be conducted during this in-person visit:*

- FMA-UE
- BBT
- ARAT
- NHPT
- mRS
- SIS-hand and ADL subsections
- In addition, the patient will be asked about interval medical history and AEs

## Deconstructing and cleaning equipment

A member of the research team will deconstruct, clean, and pack the TR system for transport back to the lab while the examiner is conducting assessments with the patient.

# Visit 4 (End of Study)

The end-of-study visit will generally be conducted at Cal Rehab, but accommodations for home assessment will be made as needed; this visit occurs 1 month after Visit 3. Visit 4 may be broken into more than one session, as needed. All Visit 4 assessments are available in a single "Visit 4" packet, located in the lab's Box folder. Details regarding administration of each assessment is found within individual CRFs.

## Assessments

The following assessments will be completed during this final in-person visit:

- ARAT
- BBT
- mRS
- FMA-UE
- NHPT
- SIS—ADL and hand subsections
- The patient will be asked about interval medical history and AEs

# Visit 5 (for UC only)

As previously mentioned, patients in the UC group will be offered a 6-week course of TR after Visit 4 (i.e., 5-6 months after stroke). For those subjects who choose to complete this training, the same assessments administered at Visit 4 will be re-assessed at Visit 5. These include the following:

- ARAT
- BBT
- mRS
- FMA-UE
- NHPT
- SIS—ADL and hand subsections
- The patient will be asked about interval medical history and AEs

# Randomization and Blinding

## Randomization

A web-based randomization procedure will be used to assign patients to one of three groups in a 3:3:2 ratio. The three treatment groups are [1] TR plus Sinemet, [2] TR plus placebo, and [3] UC.

## Blinding

With regard to TR vs. UC, study assessors will be blind to treatment assignment. Several steps will be taken to maintain this blind, including having assessments occur in a separate part of the building from TR therapy.

With regard to TR+Sinemet vs. TR+placebo, enrollees and their family members, study assessors, study treatment therapists, clinicians involved in UC, the study PI, and all other study personnel will remain blinded to type of pill assigned. The sole person unblinded to pill type (for patients randomized to either TR+Sinemet or TR+placebo) will be the study statistician. With regard to the pill to which a TR patient was assigned, the study PI will be able to break the blind at any time in case of a medical emergency requiring this knowledge. To enable this, a password-protected file and a hard copy sealed envelope will both be in the PI's possession and will remain unopened unless an emergency unblinding event arises.

# Sample Size and Statistical Analysis

## Sample Size

The primary endpoint is the ARAT, the MCID for which is 5.7 points. This study is powered for the Aim 1 analyses, which will compare [1] patients receiving TR (i.e., combining TR+Sinemet with TR+placebo) to [2] patients receiving UC. Based on a randomization distribution of 3:3:2 (TR+Sinemet, TR+placebo, UC), and using a 2-sided alpha of 0.05, this study will have 80% power to detect a mean difference between groups of 5.7 points in the change in ARAT-time, assuming a SD of 7.4 points[97, 139], with a total of 72 patients: 27 in TR+Sinemet, 27 in TR+placebo, and 18 in UC.

The study is funded to enroll 72 patients. Subject dropout may be as high as 20%, and so when possible additional patients may be enrolled.

## Statistical Analysis

We will present descriptive statistics by group for the important covariates including age, site, time from stroke to randomization, MEP status, and hours of outside rehabilitation. We will also report compliance, defined as the percentage of the 36 sessions during which patients complete more than half (≥36 min) of assigned activities. For all analyses, data not normally distributed will be appropriately transformed.

Primary efficacy analysis will use the Intent-To-Treat population, consisting of all randomized subjects and multiple imputation for missing data. Secondary analysis will examine the Per-Protocol population, defined as all subjects with complete data who complete ≥36 minutes of assigned activities on ≥30 of the 36 therapy sessions over no more than 8 weeks. Analyses will be performed using SAS and R software.

Logistic regression will be used to create a propensity score[135] for treatment group using age, time from stroke to randomization, and total hours of outside rehabilitation therapy from Visit 1 to Visit 4 (or Visit 3 when change is to visit 3). Inverse weights based on this score will be used in secondary analyses to compute adjusted change distributions and corresponding p values. The primary analyses will be based on the inverse propensity score weighted (adjusted) change from base. The corresponding unadjusted changes will also be reported as a secondary analysis. Since this is a randomized trial, we expected the primary propensity adjusted and unadjusted results to be similar.

Aim 1. TR+UC is superior to UC alone: A 6-week program of TR targeting arm movement added to UC will result in better arm function as compared to UC alone. The primary endpoint is the change in ARAT score from baseline to 1 month after end of therapy Visit 4).

The mean differences in ARAT score change from Visit 1 (baseline) to Visit 4 (1 month after end of therapy) will be compared on the log scale using an inverse propensity adjusted t test. A similar method will be used for the secondary change from Visit 1 to Visit 3 (end of therapy). We will first compare the combined TR + UC groups versus the UC group (Aim 1) and then compare TR+Sinemet+UC versus TR+placebo+UC under this model. (Aim 2). As a secondary analysis, we will report the corresponding unadjusted results.

The difference in ARAT score change between [1] the combined TR group and [2] the UC group will be computed and the distributions compared using ANCOVA, adjusting for Visit 1 ARAT score and propensity score. Specifically, this Aim will compare UC vs. the combined two TR groups (TR+Sinemet plus TR+placebo).

Exploratory analyses will examine whether aphasia or neglect affect TR efficacy by determining if the extent of aphasia (Visit 1 LAST score) or neglect (Visit 1 SCT score), respectively, is correlated with change in ARAT score from Visit 1 to Visit 4. We will use a linear regression model with ARAT change as the outcome, and with treatment group, LAST score, and propensity score as predictors in order to assess the association. This will be repeated using SCT score instead of LAST score. Restricted cubic splines will be used to determine whether the relationships of language screening and neglect to ARAT score change are each linear.

An additional exploratory analysis will examine whether results vary according to the actual TR dose (the total number of arm repetitions across the 36 treatment sessions), using similar regression methods. Sex will also be explored: while females may have poorer functional outcomes after stroke[136-138], it is unclear whether the same underlying factors predict that sex will also be associated with a poorer response to rehabilitation therapy.

Analyses will be repeated examining a secondary endpoint, BBT, and then using several tertiary endpoints (FMA-UE, CES-D, mRS, NHPT, SIS-ADL, and SIS-hand). The lead secondary endpoint is the BBT, and this will be analyzed using alpha=0.05. The tertiary endpoints are considered exploratory and will be examined without correction for multiple comparisons. The same statistical methods as above will be used except that the dependent measure will be change from Visit 1 to Visit 4 in each of the secondary/tertiary endpoints. An additional analysis will examine mRS as the dependent variable but instead using a shift analysis (ordinal logistic repeated measures regression) of mRS change score from Visit 1 to Visits 3 and 4.

To aid in the interpretation of the above analyses, additional corollary analyses will repeat above but use as the dependent measure change from Visit 1 to Visit 3. This will be done for the ARAT as well as for the FMA-UE, BBT, mRS, and SIS-hand subsection.

Aim 2. TR+Sinemet is superior to TR+placebo: Among patients randomized to TR, gains in arm function will be greater in those who take Sinemet (25/100) prior to daily TR, as compared to patients who take placebo prior to TR.

The above analyses will be repeated but instead comparing patients randomized to [1] TR+Sinemet vs. [2] TR+placebo.

Aim 3. Less CST injury and higher dopamine polygene score predict better recovery of arm function: Across all subjects, change in arm function will be highest in those with lower % CST injury and in those with higher dopamine polygene scores. These relationships will remain significant when examining only patients randomized to TR. The drug X gene score interaction term will be significant such that the slope of arm gains in relation to the polygene score will be smaller (less steep) in those receiving Sinemet.

H3A: Using linear regression, we will test whether lower % CST injury predicts higher change in ARAT score from Visit 1 to Visit 4, after controlling for baseline ARAT score and clinical measures (age, time from stroke to randomization, and total hours of outside rehabilitation therapy from Visit 1 to Visit 4). Primary analysis will examine all enrollees. Secondary analysis will examine this relationship separately for patients randomized to one of the two TR groups, while tertiary analysis will examine this separately across all three treatment groups.

Restricted cubic splines will be used to determine if the effect of continuous covariates such as age are linear. A linear model that includes individual clinical measures will be used rather than propensity adjustment so that the effect of % CST injury can be compared to the effects of the other covariates. This approach also allows us to test the hypothesis that % CST injury predicts ARAT gains beyond what can be learned from clinical variables alone.

H3B: We will test whether higher dopamine polygene score predicts higher change in ARAT score from Visit 1 to Visit 4, after controlling for the same covariates as in H3A. Analyses will follow those described in H3A.

Secondary analysis will repeat H3A and H3B using change in BBT from Visit 1 to Visit 4 as the dependent measure. Tertiary analyses will repeat these methods focusing on change in FMA-UE, CES-D, mRS, NHPT, SIS-ADL, and SIS-hand scores.

An additional H3B analysis will examine the drug X gene score interaction term in those patients randomized to TR (i.e., TR+Sinemet or TR+placebo). Based on our prior findings in healthy subjects[114], this term is hypothesized to be significant such that the slope of ARAT change in relation to the polygene score will be smaller (less steep) in those receiving Sinemet.

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